FY18 Science & Technology Efforts & Programs

PREVENTION, MITIGATION, AND TREATMENT OF BLAST INJURIES

REPORT TO THE EXECUTIVE AGENT

DoD Blast Injury Research Program Coordinating Office ■ U.S. Army Medical Research & Materiel Command

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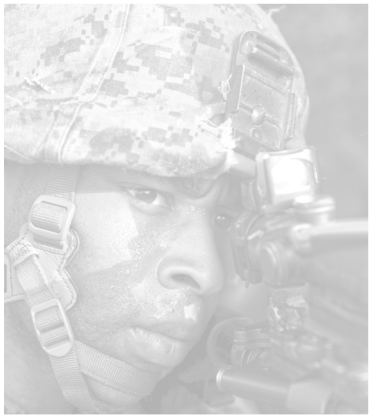

FOREWORD FROM THE DIRECTOR

The threat environment is evolving and becoming more complex as our adversaries develop and employ increasingly sophisticated weapons and tactics. However, this increasingly complex and technologically sophisticated threat environment has not diminished the long-standing and enduring threat posed by explosive weapons. Explosive weapons continue to dominate modern warfare, and the injuries they cause can be complex and catastrophic.

The complexity of blast-related injuries presents significant injury prevention, treatment, and rehabilitation challenges. The types of injuries encompassed under the umbrella headings of "blast-related injury" or "blast injury" are diverse and wide-ranging, from hemorrhage caused by penetrating fragments and traumatic amputation, to internal organ injuries from blast overpressure, to blunt impact injuries and burns. Overcoming these challenges requires the coordinated efforts of diverse medical and non-medical communities, and equally diverse scientific, medical, engineering, and operational disciplines.

The research accomplishments highlighted in this report address the entire spectrum of blast injuries, and they support the development and timely delivery of effective blast injury prevention, treatment, and rehabilitation solutions to Service members. They also illustrate the power of information sharing and collaboration. The medical and non-medical research communities responsible for these accomplishments include DoD and other Federal laboratories, academia, and industry, both domestic and international. These accomplishments are as wide-ranging as the injuries they address. Some examples which are highlighted in this report include a novel approach to preventing and treating blast-related hearing loss, evidence-based standards for safe exposures to blast overpressure during repeated heavy weapons firing, nutritional countermeasures for blast-related traumatic brain injury (TBI) and post traumatic stress disorder (PTSD), a promising synthetic platelet substitute that can significantly reduce uncontrolled hemorrhage and coagulopathy in prolonged field care scenarios, precision medicine approaches to treating chronic mild TBI (mTBI), and improved prostheses for Service members with blast-related limb loss.

In addition to highlighting noteworthy blast injury research accomplishments, this annual report describes the initiatives of the DoD Blast Injury Research Program Coordinating Office (PCO) which was established in 2007 at the U.S. Army Medical Research and Materiel Command to support the DoD Executive Agent (EA) for blast injury research. The EA and the PCO have their origins in Public Law and DoD Directive. In 2006, Congress and senior DoD leaders recognized the need for better communication and collaboration among fragmented blast injury research communities and programs, and the benefit of designating a DoD EA with responsibility for facilitating information sharing and collaboration among these communities.

Since 2007, the PCO has been leading efforts to break down communication barriers, enable information sharing, and facilitate collaboration among diverse stakeholders to address and develop solutions to complex blast injury challenges. Among these efforts is the BIPSR Process that brings together stakeholders from the medical, operational, and materiel development communities to ensure that the DoD is using the best

available science-based guidelines for developing effective blast injury protective equipment for Service members. The International State-of-the-Science Meeting Series is leveraging the expertise of the world's best scientists, engineers, and clinicians to identify blast injury knowledge gaps and to recommend research and policies that will close the gaps. The DoD Working Group on Computational Modeling of Human Lethality, Injury, and Impairment, and a related, PCO-led, NATO Human Factors and Medicine Research Task Group (HFM-270) are developing a conceptualized framework with component models capable of providing threat-to-outcome modeling and simulation of the effects of blast on the human that will make it possible to rapidly develop and test novel blast protective equipment in a virtual environment. Finally, the historical blast bioeffects research data recovery project is recovering and sharing 50 years of knowledge on the biological effects of blast to prevent unnecessary duplication of effort.

The PCO has responded to the Congressional mandate for the EA to leverage the knowledge and expertise of blast injury experts from other countries to address the DoD's blast injury challenges. The PCO led the nine-nation NATO HFM-234 Research Task Group which published much needed guidelines for conducting blast injury research that will enable high quality research and advance our understanding of blast injuries. The PCO's Japan-U.S. Technical Information Exchange Forum on Blast Injury (JUFBI) has evolved to become the International Forum on Blast Injury Countermeasures (IFBIC), an international forum that will leverage the blast injury research expertise from many nations. Finally, the PCO is leading a collaborative research project with India under the U.S.-India Defense Technology and Trade Initiative to develop computational and experimental models of mTBI that will guide the development of blast injury protective equipment and treatment strategies.

Looking to the future, it is clear from the lessons of the past that only a continuing and concerted blast injury research coordination effort can prevent returning to a time when fragmented and stovepiped research programs, and communication barriers impeded the development of timely solutions to emerging blast injury threats. The PCO is committed to building upon its past successes by working diligently with its vast network of stakeholders to identify new opportunities for multi-community, multi-disciplinary collaboration and information sharing that will advance the state of the science and accelerate the delivery of blast injury prevention and treatment solutions to Service members who are the ultimate and most deserving beneficiaries of a coordinated DoD blast injury research program.

As I draw to a close more than four decades of military and civilian service, I would like to express my sincere thanks to the Service members and selfless public servants with whom I have had the distinct honor and privilege to serve and support. I am grateful that for the past 21 years of my career, I have had the opportunity to work alongside talented scientists, engineers, medical practitioners, and military operational experts who are responsible for so many significant advancements in blast injury prevention, treatment, and rehabilitation. I am equally honored and humbled that for the past 12 years I have had the unique opportunity and distinct honor to lead a team of dedicated and mission-focused professionals who are responsible for the PCO's significant accomplishments. Finally, and most importantly, I am grateful to the dedicated men and women of our Armed Forces, past, present, and future, who selflessly sacrifice in service to this great Nation.

Michael J. Leggieri, Jr.
Director, DoD Blast Injury Research Program Coordinating Office
U.S. Army Medical Research and Materiel Command

ACKNOWLEDGMENTS

The DoD Blast Injury Research Program Coordinating Office is enormously grateful to the many individuals and organizations across the DoD who contributed to this report and the work it summarizes (see list on next page). Particular recognition goes to the collaborative science and technology efforts that are leading the way toward improved strategies for the prevention, mitigation, and treatment of blast injuries. The dedication of the scientists, clinicians, engineers, and operators who support DoD blast injury research represent a commitment to the health and well-being of Service members and their Families. In addition, we would like to thank the reviewers for their valuable insights and feedback.

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EXECUTIVE SUMMARY

Blast-related injury has become increasingly common in recent conflicts, including Operation Enduring Freedom (OEF), Operation Iraqi Freedom (OIF), and Operation New Dawn (OND). Improvised explosive devices (IEDs) remain the weapon of choice for militant groups worldwide, with resulting civilian and military injuries that span from mild to severe. Although technological advances and tactical improvements have improved survival rates, blast events leave Service members with significant injuries including hearing loss, penetrating injuries, burns, fractures and traumatic amputations, and open and closed head injuries including traumatic brain injury (TBI). Even relatively mild symptoms of blast injuries (for example, tinnitus, dizziness, or disorientation) can have major effects on operational readiness and quality of life (QOL). To address these effects, the United States (U.S.) Department of Defense (DoD) invests significant resources in medical and nonmedical research on the prevention, mitigation, and treatment of blast injuries.

In Section 256 of Public Law 109-163, National Defense Authorization Act (NDAA) for Fiscal Year 2006 (FY06), Congress directed the Office of the Secretary of Defense (OSD) to designate an Executive Agent (EA) to coordinate DoD medical research efforts and programs relating to the prevention, mitigation, and treatment of blast injuries. DoD Directive (DoDD) 6025.21E formalized the DoD's blast injury research efforts. This directive established the DoD Blast Injury Research Program and assigned EA responsibilities to the Secretary of the Army. These responsibilities also include recommending blast injury prevention standards, ensuring DoD-sponsored blast injury research programs address the Services' needs, and sharing blast injury research information among medical and nonmedical communities. Prior to FY18, the responsibility to execute EA responsibilities was delegated to The Surgeon General of the U.S. Army (TSG), and the Blast Injury Research Program Coordinating Office (PCO) was established at the U.S. Army Medical Research and Materiel Command (USAMRMC), Fort Detrick, Maryland, to assist in fulfilling the EA's assigned responsibilities and functions. Chapter 1 of this Report presents an overview of the DoD blast injury research community and of the delegation of EA authority effective in FY18.

Chapters 2–4 of this Report present the FY18 activities of the PCO. As demonstrated by the work detailed therein, the PCO continues to successfully accomplish our mission in support of the EA for Medical Research for the Prevention, Mitigation, and Treatment of Blast Injuries. Our success is largely due to our unique ability to cultivate strong relationships with the DoD medical and nonmedical communities, other government agencies, and international partners, and to leverage these relationships to work collaboratively to solve the many complex problems associated with the prevention and treatment of blast-related injuries.

Two significant events occurred during FY18 that impact the PCO mission. Firstly, on November 14, 2017, TSG delegated authority to Commander, USAMRMC, to act as the EA Responsible Official for Medical Research for the Prevention, Mitigation, and Treatment of Blast Injuries and to act on her behalf for all EA responsibilities, functions, and authorities. This change has strengthened the PCO's relationship with the medical research community and made our communication with the EA more efficient and more effective. Secondly, on December 12, 2017, the President of the United States signed the FY18 NDAA into law. Section 734 requires the Secretary of Defense (SECDEF) to conduct a longitudinal medical study on the effect of blast pressure exposure on members of the Armed Forces

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during combat and in training. The Office of the Assistant Secretary of Defense for Health Affairs (OASD(HA)) was assigned as the responsible agency to respond to this requirement. The PCO will assist OASD(HA) by using our established contract with MITRE Corporation. Fully supporting the FY18 NDAA effort is a challenge because it pulls a significant amount of the PCO contracted MITRE Corporation resources away from other PCO initiatives. Nevertheless, the PCO is committed to providing the best tools possible to OASD(HA).

In addition to the FY18 NDAA, Section 734 support, the PCO initiated another new effort during FY18. We established the Neuroscience, Neurotrauma, and Neurodegeneration Working Group (N3WG) at USAMRMC to improve collaboration and communication between the many USAMRMC organizations conducting research and developing products to treat and manage all types of brain health disorders. This group has worked together to address many complex issues involving multiple aspects of brain injury research and product development. The N3WG has enabled the USAMRMC to speak to external stakeholders with a single, coordinated voice on brain health research and development issues.

Throughout FY18, the PCO continued to make significant progress in our existing, long-term initiatives. Among these initiatives is the Blast Injury Prevention Standards Review (BIPSR) process. This initiative brings together stakeholders from medical, operational, and materiel development communities to ensure that the DoD is using the best available science-based guidelines for developing effective blast injury protective equipment for Service members. This is discussed in more detail in Chapter 4. During FY18, we reviewed candidate standards for preventing auditory injury and began the BIPSR process for dermal burn injuries. Another initiative is the International State-of-the-Science (SoS) Meeting Series which leverages the expertise of the world's best scientists, engineers, and clinicians to identify blast injury knowledge gaps and to recommend research and policies that will close the gaps. In FY18, we held a SoS meeting on the "Neurological Effects of Repeated Exposure to Military Occupational Blast" and the findings and recommendations will be used to inform the OASD(HA)-led efforts to address the FY18 NDAA, Section 734 requirements. The PCO is also chairing the DoD Working Group on Computational Modeling of Human Lethality, Injury, and Impairment, and a related, PCO-led, North Atlantic Treaty Organization (NATO) Human Factors and Medicine Research Task Group (HFM-270), which are developing a conceptualized framework with component models capable of providing threat-to-outcome modeling and simulation of the effects of blast on the human that will make it possible to rapidly develop and test novel blast protective equipment in a virtual environment. Finally, the historical blast bioeffects research data recovery project is making available 50 years of knowledge on the biological effects of blast to prevent unnecessary duplication of effort.

The PCO also had significant accomplishments with our international initiatives during FY18, which are detailed in Chapter 3. These initiatives address the Congressional mandate for the EA to leverage the knowledge and expertise of blast injury experts from other countries to address the DoD's blast injury challenges. The PCO led the nine-nation NATO HFM-234 Research Task Group (RTG), which published much needed guidelines for conducting blast injury research that will enable high quality research and advance our understanding of blast injuries. The PCO's Japan-U.S. Technical Information Exchange Forum on Blast Injury (JUFBI) evolved to become the International Forum on Blast Injury Countermeasures (IFBIC), a meeting forum that will leverage the blast injury research expertise from many nations to address blast injury issues of importance to the DoD. Finally, the PCO continued to lead a collaborative research

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project with India under the U.S.-India Defense Technology and Trade Initiative to develop computational and experimental models of mild traumatic brain injury (mTBI) that will guide the development of blast injury protective equipment and treatment strategies.

This Report features significant advances made by the innovative and dedicated members of the DoD blast injury research community with whom this Office coordinates. Chapter 5, contributed by Dr. David Tribble of the Infectious Disease Clinical Research Program (IDCRP), highlights blast-related infectious disease research and the use of the Trauma Infectious Disease Outcomes Study (TIDOS) to generate information about wound infection in injured warfighters and to improve clinical practice for the management of infectious disease. Chapter 6 presents an ongoing project of the PCO to make the valuable historical data on the biological effects of explosive blast, generated at the Albuquerque Blast Test Site on Kirtland Air Force Base from 1951-1998, available for use by the modern DoD blast injury research community. Chapter 7 is a broad survey of blast injury research advances made in FY18 by medical and nonmedical scientists, engineers, and technicians across the DoD research community, and constitutes an awe-inspiring look at the diversity and power of the tools being developed to prevent, to mitigate, and to treat blast injuries to the American warfighter.

This Report concludes with a discussion of both the immediate future, and the road ahead for DoD blast injury research. The PCO will continue to use our unique capabilities and talented staff to lead efforts that break down communication barriers, enable information sharing, and facilitate collaboration among diverse stakeholders to address and develop solutions to complex blast injury challenges. Further, we will continue to move our U.S. and international initiatives forward and apply our capabilities to any new challenges presented to us in the coming year.

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CHAPTER 1:

INTRODUCTION

Blast injuries are complex physical traumas resulting from explosions. Blast injury ranges from hearing loss and internal organ damage to traumatic brain injury, vision loss, and burns. Patients exposed to blasts often exhibit more than one of these injury types simultaneously, making their treatment highly complex. This complexity necessitates ongoing blast injury research and knowledge sharing between civilian and military sectors to speed research and development of technology to prevent and treat blast injuries.

Weapons with a blast component were responsible for 82 percent of U.S. Service members killed in action (KIA) and 86 percent wounded in action (WIA) in Iraq and Afghanistan between December 2001 and September 2017. During this time, for each KIA there were 8.4 WIA, and of those wounded, five percent suffered traumatic extremity loss (*JTAPIC, 2017*). While explosives built and/or detonated by insurgent adversaries occupy a substantial portion of blast-related injuries to U.S. Service members, preliminary evidence suggests that repeated, low-level blast exposure due to occupational training (*e.g.*, breaching) or heavy munitions firing may cause transient physical or psychological changes. This controversial topic was addressed thoroughly during the 2017 International State-of-the-Science (SoS) Meeting; it was deduced that applicable research is in its nascent stages and definitive conclusions cannot yet be drawn.

Civilians are also affected by the use of explosive devices in acts of terror. On April 15, 2013, three people were killed and 264 were wounded (including 16 who lost limbs) when homemade pressure-cooker explosives were detonated during the Boston Marathon. A terrorist attack using an explosive device took place on the Saint Petersburg Metro on April 3, 2017. Seven people were killed instantly, eight more died from their injuries, and 64 others suffered non-fatal injuries. On the evening of May 22, 2017, a lone suicide bomber detonated explosives as teenage fans were leaving a concert at the Manchester Arena in the United Kingdom (UK). The attack killed 23 and injured 800 others. An explosive, wrapped in a plastic bag that was concealed in a bucket, detonated during the morning rush on September 17, 2017 in a train attack at the Parsons Green station of the London Underground. Over 30 people suffered injuries, including burns and fractures.

FIGURE 1-1: Assignment of EA Authority

* During FY18, the Under Secretary of Defense for Acquisition, Technology and Logistics (USD(AT&L)) was reorganized to include the Under Secretary of Defense for Acquisition and Sustainment (USD(A&S)) and the Under Secretary of Defense for Research and Engineering (USD(R&E))

The impact of explosive devices on U.S. military operations, Service members, their Families, and civilian victims of conflict and terrorism, emphasizes the need for coordinated research investments on the prevention, treatment, and rehabilitation of blast injuries.

In 2006, Congress passed legislation to address critical gaps associated with blast injury research. In Section 256 of Public Law 109-163, National Defense Authorization Act (NDAA) for fiscal year 2006 (FY06), Congress directed the Office of the Secretary of Defense (OSD) to designate an Executive Agent (EA) to coordinate Department of Defense (DoD) medical research efforts and programs relating to the prevention, mitigation, and

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treatment of blast injuries (Figure 1-1). In response to this direction, Department of Defense Directive (DoDD) 6025.21E, Medical Research for Prevention, Mitigation, and Treatment of Blast Injuries, formally established the DoD Blast Injury Research Program on 5 July 2006 (see Appendix C: DoDD 6025.21E).

DoDD 6025.21E assigns the Assistant Secretary of Defense for Research and Engineering (ASD(R&E)) with oversight of the Blast Injury Research Program and designates the Secretary of the Army (SECARMY) as the DoD EA.

SECARMY delegated authority and assigned responsibility to execute EA responsibilities directly to The Surgeon General of the U.S. Army. The Surgeon General of the U.S. Army delegated this authority to the Commander, USAMRMC.

The PCO, established in 2007, supports the EA by coordinating relevant DoD medical research efforts and programs. Its role includes facilitating collaboration, identifying blast injury knowledge gaps, shaping medical research programs to fill identified gaps, disseminating blast injury research information, and promoting information sharing and partnerships among DoD and non-DoD entities (Figure 1-2). Through these efforts, the PCO works to improve blast injury prevention, mitigation, and treatment strategies for Service members and their Families.

Responsibilities and Functions

DoDD 6025.21E assigns key DoD components with specific responsibilities to coordinate and manage the medical research efforts and DoD programs related to the prevention, mitigation, and treatment of blast injuries. The following is a summary of the responsibilities assigned by the Directive. For a more detailed description, please see Appendix C: DoDD 6025.21E.

- **The ASD(R&E)** establishes procedures to ensure new technology developed under the DoDD is effectively transitioned and integrated into systems and transferred to DoD components; chairs the Armed Services Biomedical Research, Evaluation and Management (ASBREM) Community of Interest (COI); oversees the functions of the DoD EA; and serves as the final approving authority for DoD blast injury research programs.

FIGURE 1-2: Breadth of the PCO's Coordinating Responsibilities

Joint Improvised-Threat Defeat Agency (JIDA); Joint Non-Lethal Weapons Directorate (JNLWD); Technical Support Working Group (TSWG); North Atlantic Treaty Organization (NATO); Uniformed Services University of the Health Sciences (USU); United States Special Operations Command (USSOCOM); Defense Advanced Research Projects Agency (DARPA)

- **The Assistant Secretary of Defense for Health Affairs (ASD(HA))** assists in requirements development; assesses and coordinates relevant research efforts to resolve capability gaps; approves Military Health System (MHS) blast injury prevention, mitigation, and treatment standards; appoints representatives to DoD EA coordination boards and committees; and ensures the information systems' capabilities of the MHS support the EA.

- **The SECARMY** was designated as the DoD EA for Medical Research for Prevention, Mitigation, and Treatment of Blast Injuries. In 2017, the Surgeon General designated this authority to the Commander, USAMRMC.

- **The Commander, USAMRMC,** as the delegated EA, coordinates and manages DoD blast injury research efforts and programs by:
  - Maintaining a DoD technology base for medical research related to blast injuries
  - Performing programming and budgeting actions for all blast injury research based on analysis and prioritization of DoD component needs
  - Providing medical recommendations on MHS blast injury prevention, mitigation, and treatment standards
  - Executing the approved DoD Blast Injury Research Program
  - Ensuring that blast injury research information is shared

- **The Secretary of the Navy and the Secretary of the Air Force** assist in requirements development and coordinate all blast injury research efforts and requirements through the EA.

- **The President of the Uniformed Services University of the Health Sciences (USU)** ensures education relating to blast injury prevention, mitigation, and treatment is included in the USU medical education curriculum and programs. The USU President coordinates all blast injury research efforts and requirements through the EA, and appoints representatives to any coordination boards or committees related to blast injury research.

- **The Chairman of the Joint Chiefs of Staff** coordinates all blast injury efforts and requirements through the EA, appoints a senior member to the Armed Services Biomedical Research Evaluation and Management (ASBREM) Communities of Interest (COI), and appoints representatives to any coordination boards or committees related to blast injury research.

- **The Commander, U.S. Special Operations Command (USSOCOM)** establishes procedures for the coordination of Defense Major Force Program II activities with those of the EA, forwards the Command's approved blast injury research requirements to the DoD EA, and appoints representatives to the ASBREM COI and any other coordination boards or committees related to blast injury research.

- **The Joint Improvised-Threat Defeat Agency (JIDA),** supported the development, maintenance, and usage of a joint database on the efficacy of in-theater personal protective equipment (PPE) and vehicular equipment designed to protect against blast injury by helping to establish the Joint Trauma Analysis and Prevention of Injuries in Combat (JTAPIC) Program of USAMRMC. The JTAPIC Program fulfills the intent of a "joint database" by providing a process that enables data sharing and analysis across communities. Continuing responsibilities include identifying related operational and research needs, coordinating research efforts to resolve capability gaps, and appointing representatives to the ASBREM COI and any other coordination boards or committees related to blast injury research.

TABLE 1-1: Taxonomy of Injuries from Explosive Devices

Injury Type	Description
Primary Blast Injuries: • Blast lung • Ear drum rupture and middle ear damage • Abdominal hemorrhage and perforation • Eye rupture • Non-impact induced mild traumatic brain injury	Primary blast injuries result from the high pressures created by the blast. These high pressures, known as blast overpressure (BOP), can crush the body and cause internal injuries. Primary blast injuries are the only injury classification that is unique to blast. 
Secondary Blast Injuries: • Penetrating ballistic (fragmentation or blunt injuries) • Eye penetration • Mild and severe brain injury	Secondary blast injuries result when strong blast winds behind the pressure front propel fragments and debris against the body and cause blunt force and penetrating injuries. 
Tertiary Blast Injuries: • Fracture and traumatic amputation • Closed and open brain injury • Blunt injuries • Crush injuries	Tertiary blast injuries result from strong winds and pressure gradients that can accelerate the body and cause the same types of blunt force injuries that would occur in a car crash, fall, or building collapse. 
Quaternary Blast Injuries: • Burns • Injury or incapacitation from inhaled toxic fire gases	Quaternary blast injuries are the result of other explosive products (such as heat and light) and exposure to toxic substances from fuels, metals, and gases that can cause burns, blindness, and inhalation injuries. 
Quinary Blast Injuries: • Illnesses, injuries, or diseases caused by chemical, biological, or radioactive substances	Quinary blast injuries refer to the clinical consequences of post-detonation environmental contaminants, including chemical, biological, and radioactive substances (e.g., dirty bombs). 

from DoDD 6025.21E

DoD Framework for Characterizing Blast Injuries

The EA plays a key role in coordinating research and development for the entire spectrum of blast injury that can result from exposure to explosive weapons, such as hearing loss, penetrating injuries, burns, fractures, traumatic amputations, and open and closed head injuries. The DoD adopted the *Taxonomy of Injuries from Explosive Devices,* as defined in DoDD 6025.21E, to provide a common framework for characterizing the full spectrum of blast injuries. The *Taxonomy of Injuries from Explosive Devices* assigns blast injuries to five categories—Primary, Secondary, Tertiary, Quaternary, and Quinary—based on the mechanism of injury (Table 1-1).

Blast Injury Research Program Areas

DoD blast injury research works to close knowledge gaps in the prevention, mitigation, and treatment of blast injuries. To address the gaps and capability requirements for the full spectrum of blast injuries, current research efforts must actively pursue new tools and understanding in each of three research areas: Injury Prevention, Acute Treatment, and Reset (Figure 1-3).

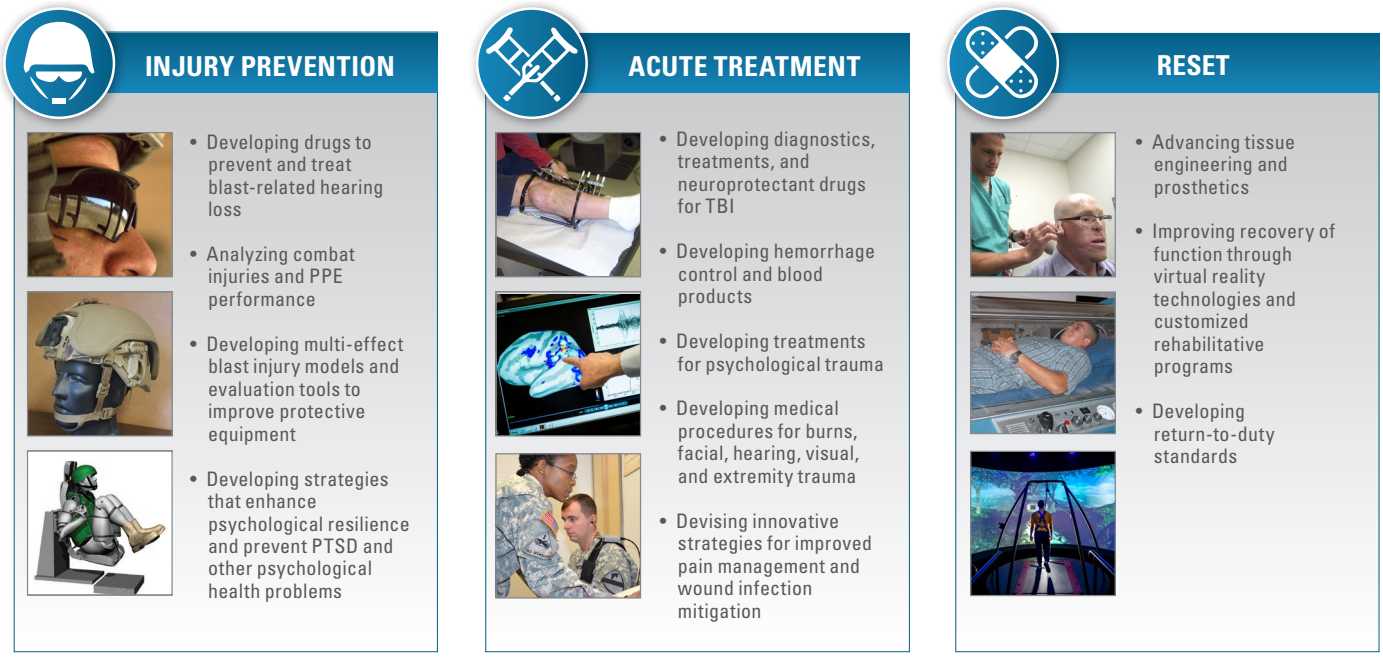


FIGURE 1-3: Blast Injury Research Program Areas

Photo credits: Column 1—U.S. Marine Corps, U.S. Naval Research Laboratory, U.S. Army; Column 2—U.S. Army Medical Command, U.S. Army Medical Research and Materiel Command, U.S. Army; Column 3—U.S. Air Force, Defense Advanced Research Projects Agency, Defense Centers of Excellence.

Injury Prevention

Injury prevention reduces the risk of blast injuries. This research program area provides medically-based design guidelines and performance standards for individual and combat platform occupant protection systems; comprehensive injury surveillance systems that link injury, operational, and protection system performance data; tools to identify individual susceptibility to injury; and individual training to prevent or mitigate injuries.

Acute Treatment

Research and development in the area of **acute treatment** is intended to improve survivability and to mitigate long-term disability for Service members suffering from the full spectrum of injuries following blast events. The acute treatment research program area explores development of new diagnostic tools, interventions for hemorrhage control and resuscitation, strategies to minimize wound infection, and tools and guidelines for eye injuries. This research program area will lead to a greater understanding of the capabilities and limitations of current technologies; new tools and validated methods for injury mitigation in the prehospital setting; and improved diagnostics and clinical guidelines for the acute treatment of blast injuries.

Reset

Research and development in the area of **reset** aims to mitigate disability by providing a biomedically-based performance assessment capability for return-to-duty (RTD) and redeployment following injury; rebuilding full performance capabilities in redeployed individuals; and restoring function and ability to seriously injured Service members with prosthetic devices. The term “reset” acknowledges a concept that extends beyond rehabilitation to include all activities necessary to return injured Service members to duty or to productive civilian lives.

Coordination of Blast Injury Research Activities

Numerous DoD organizations include blast injury research in their mission scope, but no single organization covers the entirety of the field. Therefore, promoting and maintaining effective coordination among these groups is essential to achieving gains in injury prevention, acute treatment, and reset after injury. Congress directed DoD to establish an EA for this purpose, and the Blast Injury Research PCO has been supporting the EA in this mission since 2006.

DoD blast injury research efforts are requirements-driven and fill knowledge gaps in preventing and treating injury, as well as restoring function. To address identified gaps, researchers work with stakeholders from across the blast injury research community. Examples of programs and collaborative efforts supporting blast injury research are discussed below.

DoD Component Services and Agency Research Programs

Each of the Services and the Defense Advanced Research Projects Agency (DARPA) have blast injury research programs primarily funded through the President's Budget. These programs sponsor research internally, within DoD laboratories and clinical centers, and externally through academic and industry partnerships. DoD blast injury research focus areas include injury surveillance, combat casualty care (CCC), wound infections, military operational medicine (MOM), and clinical and rehabilitative medicine.

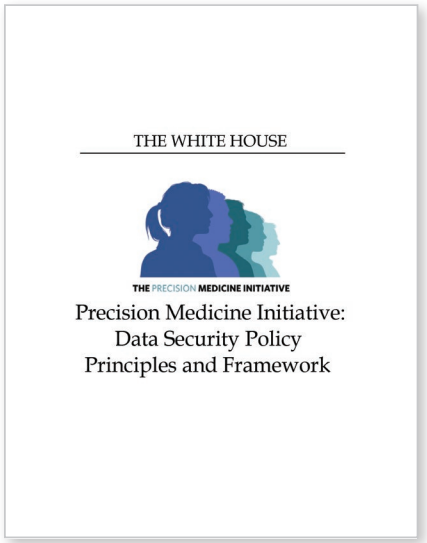
Defense Health Agency Research and Development Directorate

Established in FY14 by the Office of ASD(HA), the Defense Health Agency Research and Development (DHA R&D) Directorate oversees medical research, development, testing, and evaluation (RDT&E) programs related to the healthcare needs of Service members. The DHA R&D Directorate manages the RDT&E funds of the Defense Health Program (DHP). Joint Program Committees (JPC), which consist of DoD and non-DoD technical experts, make funding recommendations for research and manage research programs under the DHA R&D Directorate in diverse military medical program areas, including those that directly address blast injuries (see Table 1-2).

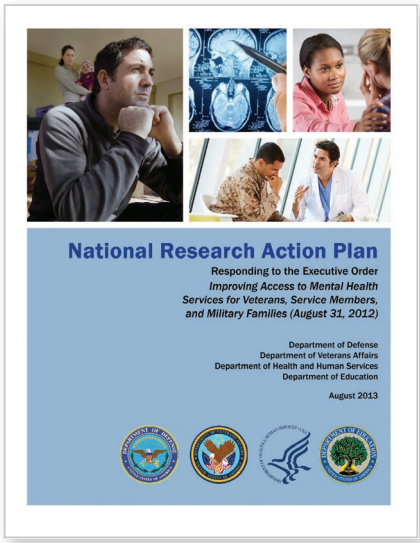
TABLE 1-2: Joint Program Committees

JPC	DHA R&D Directorate Program Areas	Examples of Research Focus Areas
JPC-1	Medical Simulation and Information Sciences	• Medical Simulation • Health Information Technology and Informatics
JPC-2	Military Infectious Diseases	• Wound Infections (Prevention, Management, and Treatment) • Pathogen Detection
JPC-5	Military Operational Medicine	• Psychological Health and Resilience • Hearing Loss • Injury Prevention
JPC-6	Combat Casualty Care	• Damage Control Resuscitation • Mild, Moderate, Severe, and Penetrating TBI • Burn Injury • En Route Care
JPC-7	Radiation Health Effects	• Diagnostic Biodosimetry • Countermeasures (Protection and Treatment)
JPC-8	Clinical and Rehabilitative Medicine	• Neuromusculoskeletal Injury • Acute and Chronic Pain Management • Regenerative Medicine • Sensory Systems

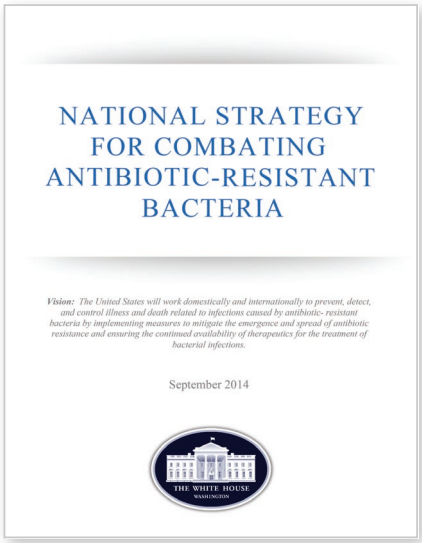
FIGURE 1-4: White House Initiatives Related to Blast Injuries



Precision Medicine Initiative
(White House)



The National Research Action Plan for Improving Access
to Mental Health Services for Veterans,
Service Members, and Military Families
(U.S. DoD, VA, DHHS, and U.S. Department of Education)



National Strategy for Combating
Antibiotic-Resistant Bacteria
(White House)

These collaborative research programs rely on expertise and capabilities from across the Services, U.S. Department of Veterans Affairs (VA), U.S. Department of Health and Human Services (DHHS), academic centers, industry partners, and other scientific and technical communities.

The current emphasis of the DHA R&D Directorate is on the SECDEF's stated priorities: post traumatic stress disorder (PTSD), traumatic brain injury (TBI), prosthetic devices, restoration of eyesight and advancing eye care, and other conditions relevant to battlefield injuries and ailments that affect both Service members and their Families. These priorities stem from the Precision Medicine Initiative (Figure 1-4); the National Research Action Plan (NRAP; Figure 1-4) for Improving Access to Mental Health Services for Veterans, Service members, and Military Families; the National Strategy for Combating Antibiotic Resistant Bacteria (Figure 1-4); and international scientific partnerships that facilitate global health engagement. The DoD Blast Injury Research Program works with Military Operational Medicine Research Program (MOMRP; JPC-5), Combat Casualty Care Research Program (CCCRP; JPC-6), and Clinical and Rehabilitative Medicine Research Program (CRMRP; JPC-8) to support research that falls within these priorities.

Congressionally Directed Medical Research Programs

The Congressionally Directed Medical Research Programs (CDMRP) is a global funding organization managing programs in cancer research, military medical research, and other disease- and injury-specific research areas. CDMRP represents a unique partnership between the U.S. Congress, the Military, and the public that uses congressionally directed dollars and core dollars (presidential budget appropriation) to fund groundbreaking, high-impact research awards. The CDMRP works collaboratively with the DHA R&D Directorate, USAMRMC, and other members of the federal and non-federal medical research community to direct its investment in meritorious research that targets critical gaps, including several in areas that are highly relevant to blast injury research. Appendix D: Supplemental Tables

lists the CDMRP research programs supporting blast injury research.

Centers of Excellence

In response to congressional requirements within the NDAA, the DoD established several clinical Centers of Excellence (CoEs). These centers seek to improve clinical care capabilities using new and updated clinical practice guidelines (CPG) and policy recommendations, to understand injury and outcome trends, and to inform research sponsors about the needs and requirements of the clinical communities. As a part of their mission, a number of CoEs address blast injury research including: the Defense Center of Excellence for Psychological Health and Traumatic Brain Injury (DCoE), Defense and Veterans Center for Integrative Pain Management, Hearing Center of Excellence (HCE), Extremity Trauma and Amputation Center of Excellence (EACE), National Intrepid Center of Excellence (NICOE), and Vision Center of Excellence (VCE).

Research Forums, Consortia, and Programs Supporting Blast Injury Research

Numerous ongoing collaborative efforts in the DoD (*e.g.,* working groups, consortia, research programs) are also investigating blast injuries and associated health outcomes. These efforts include the development of new blast injury protective or preventive measures, the development of new treatments for blast injury, and improvements in post traumatic rehabilitation. For example, the Chronic Effects of Neurotrauma Consortium (CENC) targets mild TBI (mTBI; including blast-related mTBI) to address knowledge gaps in the basic sciences, determine the effects of mTBI on late-life outcomes and neurodegeneration, identify Service members most susceptible to these effects, and identify potentially effective treatment strategies. Table 1-3 contains additional examples of collaborative research efforts.

Preview of this Report

The following chapters highlight research efforts to advance the DoD's ability to prevent, mitigate, and treat blast injury.

- Chapter 2 describes the PCO's activities within the five key EA Mission Thrust Areas: facilitating collaboration, identifying blast injury knowledge gaps, disseminating blast injury research information, shaping research programs to address knowledge gaps, and promoting information sharing and partnerships.

- Chapter 3 describes some of the PCO's international collaborative efforts, including leading the NATO Human Factors and Medicine (HFM)-RTG 270 and successful completion of the NATO HFM-234 (RTG).

- Chapter 4 focuses on how the PCO is advancing the MHS Blast Injury Prevention Standards Recommendations (BIPSR) Process.

- Chapter 5 presents an in-depth look at the blast injury-related work of the Infectious Disease Clinical Research Program (IDCRP), discussing the context of historical blast-related infection, current efforts at IDCRP, and significant research challenges.

- Chapter 6 gives an overview of the PCO's efforts to preserve, validate, and disseminate data from the historically valuable medical blast injury studies conducted at the Blast Test Site located at Kirtland Air Force Base from 1951 until 1998.

- Chapter 7 presents the latest accomplishments in blast injury RDT&E supported by the DoD. These accomplishments include scientific advancements, improvements in standards of care, and the development of products to prevent, diagnose, and treat blast injuries.

- Chapter 8 is a discussion of the way forward for the Blast Injury Research Program in coordinating and supporting future advancements in blast injury research.

TABLE 1-3: Examples of DoD Research Forums, Consortia, and Programs Supporting Blast Injury Research

DoD Entity	Blast Related Efforts
Armed Forces Institute of Regenerative Medicine	The multi-institutional, multi-disciplinary **Armed Forces Institute of Regenerative Medicine (AFIRM)** collaborates across numerous agencies to accelerate the development of diagnostic products and therapies for severely wounded Service members in need of reconstructive treatments. Currently, AFIRM represents 60 projects spread across 33 academic, corporate, and tri-service research institutions.
Auditory Fitness For Duty Working Group	One of the priorities of the **Auditory Fitness For Duty Working Group (AFFD WG)** is to assess occupations and identify hearing-critical tasks within the military. A hearing-critical task is defined as a task in which the detection of sound, understanding of speech, and/or localization of sound are essential for successful accomplishment of action. The AFFD WG also supports HCE's mission to heighten readiness and continuously improve the health and quality of life (QOL) of Service members and Veterans through advocacy and leadership in the development of initiatives focused on the prevention, diagnosis, mitigation, treatment, rehabilitation, and research of hearing loss and auditory-vestibular injury.
Bridging Advanced Developments for Exceptional Rehabilitation Consortium	The **Bridging Advanced Developments for Exceptional Rehabilitation (BADER) Consortium** works with military treatment facilities, VA centers, academia, and industry leaders to target orthopedic care after blast injury. Special areas of interest include improving amputee gait, prescription of prosthetics, and QOL issues following extremity injury.
Center for Neuroscience and Regenerative Medicine	**Center for Neuroscience and Regenerative Medicine (CNRM)** was established by Congressional action (Public Law 110-252) as an intramural federal TBI research program focused on the study of blast injury to the brain and post traumatic stress in warfighters. Today, the CNRM involves over a hundred federal intramural investigators in the National Capital Area from within the DoD and the NIH. The CNRM truly acts as a research "center" which integrates the expertise of clinicians and scientists across numerous disciplines to catalyze innovative approaches to TBI research. The CNRM research programs have an emphasis on aspects of high relevance to the military populations, particularly Service members cared for at the Walter Reed National Military Medical Center (WRNMMC) and those exposed to blast events. USU is responsible for the overall operational and fiscal management of the CNRM, on behalf of the DoD.
Chronic Effects of Neurotrauma Consortium	The **Chronic Effects of Neurotrauma Consortium (CENC)** is a dedicated joint DoD and VA effort addressing the long term consequences of mTBI in Service members and Veterans. It is conducted in response to the Presidential Executive Order 13625 and aligned to the National Research Action Plan (NRAP) for Improving Access to Mental Health Services for Veterans, Service members, and Families. The CENC Coordinating Center is located at Virginia Commonwealth University and executes 10 studies and five integrated research cores across 30 participating institutions (https://cencstudy.org). The majority of studies are focused on human subjects recruited from Veterans, Active Duty Service members, Reserve, and National Guard populations. CENC studies examine chronic TBI and comorbidities associated with mTBI including: psychological, neurological, sensory deficits (visual, auditory, vestibular), movement disorders, pain (including headache), cognitive, and neuroendocrine deficits.
Collaborative Auditory Vestibular Research Network	The **Collaborative Auditory Vestibular Research Network (CAVRN)** is composed of strategically aligned research laboratories, medical treatment facilities, nonprofit and foundation counterparts, industry and academic partners, international bodies, and other government centers of excellence. CAVRN holds annual meetings to collaborate on areas of hearing and balance issues that Service members and Veterans face as a result of their military service. This growing research network works to advance the community's understanding, spur innovation, encourage interdisciplinary collaboration, and overcome system barriers that may otherwise challenge research.

DoD Entity	Blast Related Efforts
The Consortium to Alleviate PTSD	**The Consortium to Alleviate PTSD (CAP)** is a joint VA and DoD effort to understand and treat PTSD and related conditions in Active Duty Service members and Veterans. The primary CAP objectives are to focus on the advancement of treatment strategies for PTSD and to identify and confirm clinically relevant biomarkers as diagnostic and prognostic indicators of PTSD and comorbid disorders.
Defense and Veterans Brain Injury Center	The **Defense and Veterans Brain Injury Center (DVBIC)** is the TBI center of excellence for the Defense Health Agency. DVBIC promotes state-of-the-science care from point-of-injury to reintegration for Service members, Veterans, and their Families to prevent and mitigate consequences of mild to severe TBI. At 22 sites supported by a Washington, D.C.-area headquarters, DVBIC treats, supports, trains, and monitors Service members, Veterans, Family members, and providers who have been, or care for those who are, affected by TBI.
Federal Interagency Traumatic Brain Injury Research Informatics System	The **Federal Interagency Traumatic Brain Injury Research (FITBIR) Informatics System** was initiated as a collaborative effort supported by the DoD CCCRP and the National Institute of Neurological Disorders and Stroke (NINDS) at the National Institutes of Health (NIH) as a secure, centralized informatics system developed to accelerate research in support of improved diagnosis and treatment for Service members and civilians who have sustained a TBI. Under the NRAP, de-identified data from DoD- and NIH-funded clinical TBI studies are required to be uploaded into FITBIR. Benefits include 1) accelerating the testing of new hypotheses, 2) allowing multi-study data aggregation to increase the statistical power, 3) providing existing comparator data, and 4) identifying patterns not easily extracted from a single study.
Interagency Explosives Terrorism Risk Assessment Working Group	The **Interagency Explosives Terrorism Risk Assessment Working Group** was created by the Department of Homeland Security to review progress on the Homeland Explosives Consequence Assessment Tool (HExCAT). The HExCAT is an end-to-end risk assessment tool that includes information from the intelligence community and law enforcement to characterize threat, vulnerability, and interdiction; consequence modeling to calculate the possible range of lethal and sub-lethal injuries, the medical response to an event, and the impact of various security and mitigation strategies.
Major Extremity Trauma and Rehabilitation Consortium	The **Major Extremity Trauma and Rehabilitation Consortium (METRC)** consists of a network of clinical centers and one coordinating center that work together with the DoD and other sponsoring agencies to conduct multicenter clinical research studies relevant to the treatment and outcomes of traumatic orthopedic injuries. The overall goal of METRC is to produce the evidence needed to establish treatment guidelines for the optimal care of the wounded warrior and ultimately to improve the clinical, functional, and quality of life outcomes of both Service members and civilians who sustain high energy trauma to the extremities.
The National Collegiate Athletic Association - DoD Grand Alliance: Concussion Assessment, Research, and Education Consortium	**The National Collegiate Athletic Association (NCAA)-DoD Grand Alliance: Concussion Assessment, Research, and Education (CARE) Consortium** is a joint DoD and NCAA research effort dedicated to studying concussion to better understand the development of injury and trajectory of recovery. The CARE Consortium has enrolled over 37,000 student athletes and service academy cadets at 30 sites. The Consortium has two study arms, the first being a clinical study focused on examining the natural history of concussion with a multi-site, longitudinal investigation of concussive and repetitive head impacts. The second arm builds upon the first arm, with a clinical study allowing for more advanced research projects, such as testing impact sensor technologies, studying potential biomarkers, and evaluating concussion with advanced neuroimaging. The CARE Consortium, and the data the team has and will continue to collect, will allow scientists to develop evidence-based approaches to understanding the risks, management, and possible treatment strategies for concussion.

DoD Entity	Blast Related Efforts
Pharmaceutical Intervention for Hearing Loss Working Group	The **Pharmaceutical Intervention for Hearing Loss (PIHL) Working Group** develops strategies for standardized analysis of potential systemic and local therapies for hearing loss prevention and rescue.
South Texas Research Organizational Network Guiding Studies on Trauma and Resilience	**South Texas Research Organizational Network Guiding Studies on Trauma and Resilience (STRONG STAR)** is a DoD-funded, multidisciplinary, and multi-institutional research consortium that develops and evaluates interventions for the detection, prevention, diagnosis, and treatment of combat-related PTSD and related conditions in Active Duty Service members and recently discharged Veterans.
TBI Endpoints Development Initiative	The **TBI Endpoints Development (TED) Initiative** is a collaborative, multidisciplinary team which seeks to advance and validate endpoints that can be used as U.S. Food and Drug Administration (FDA)-qualified outcomes such as Clinical Outcome Assessments (COAs) and blood-based and neuroimaging biomarkers in support of TBI clinical trials. Currently there are limited devices with FDA-cleared uses in TBI specific diagnostics. There are no FDA-approved drugs for TBI. The TED Initiative leverages DoD- ,NIH-, and foundation-funded research networks (e.g., Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TRACK-TBI), CENC, and the Concussion Research Consortium), infrastructure, and datasets in collaborations with the FDA towards qualification of TBI-specific biomarkers and tools. The efforts under the TED Initiative including submission to the FDA Drug Development Tools (DDT) process or the Center for Drug Evaluation and Research (CDER) and/or Medical Device Development Tools (MDDT) of the Center for Devices and Radiological Health (CDRH) pilot qualification process. This work is expected to facilitate approval and clearances of drugs and devices for TBI indications by the FDA.
U.S.-India Collaborative Project on Experimental and Computational Studies of Blast and Blunt Trauma Injury	This collaborative effort seeks to develop and to validate a blast injury animal model for mTBI using imaging techniques and histological procedures, as well as, assessing changes in behavior and cognition; to develop, to validate, and to cross-validate a computational model for blast and blunt injury; to develop anatomically accurate head/brain models for blast/brain injuries from clinical and experimental data; and to compare the blast and blunt data to develop a scaling ratio. For more information, see Chapter 3 of this report.

02

CHAPTER 2:

DOD BLAST INJURY RESEARCH PROGRAM COORDINATING OFFICE

The DoD Blast Injury Research Program Coordinating Office (PCO) supports the DoD Executive Agent (EA) by coordinating blast injury research within and outside of the DoD, nationally and internationally, to support the delivery of timely and effective blast injury prevention, mitigation, and treatment solutions for Service members. The PCO's activities help to identify and address knowledge gaps, disseminate information, and minimize duplication of effort within the DoD. The PCO promotes collaboration among researchers across the DoD, other federal agencies, academia, industry, and international partners to solve complex challenges related to blast injury. Taking full advantage of the body of knowledge and expertise that resides both within and beyond the DoD, the PCO advances blast injury research to protect and heal those who serve.

Coordination is a necessary function of DoD blast injury research because of the immense complexity and variable nature of blast injury. Across the DoD, dedicated researchers with deep domain expertise pursue technologically advanced and highly specialized solutions to individual challenges, advancing, for example, tactical measures for rapid medical evacuation, treatment guidance for infection control among blast victims, diagnostic tools for brain function, or therapeutics for severe burns. Coordination enables DoD to place these efforts within the broad landscape of blast injury research, thus empowering leaders to direct additional resources to mission-critical efforts and to identify trade-offs among them. Coordination also enables researchers to share insights and experiences across disparate lines of effort, and to identify complex dependencies: for example, is the design of personal protective equipment (PPE) adequately reflecting the patterns of blast injury seen in the field? How will the bulk and weight of new PPE affect tactics and readiness? Can multiple treatment needs be addressed by similar technologies, facilitating a reduction in field hospital footprint and complexity? The PCO's activities are chosen to encourage and to support these synergies.

MISSION

To assist in fulfilling the DoD Executive Agency responsibilities and functions related to medical research for the prevention, mitigation, and treatment of blast injuries in accordance with DoDD 6025.21E by:

- Coordinating and managing relevant DoD medical research efforts and programs
- Identifying blast injury knowledge gaps
- Shaping medical research programs to fill identified gaps
- Facilitating collaboration among diverse communities within and outside of the DoD
- Widely disseminating blast injury research information

VISION

To establish and maintain a fully coordinated DoD Blast Injury Research Program as envisioned by Congress and directed by the Secretary of Defense, that delivers timely and effective blast injury prevention, mitigation, and treatment strategies to our Service members today and in the future.

Advancing Blast Injury Research to Protect and Heal Those Who Serve

Key PCO Activities in Support of EA Mission Thrust Areas

In response to DoDD 6025.21E, Commander, MEDCOM established the PCO to assist in fulfilling EA responsibilities and functions to coordinate DoD blast injury research efforts and programs. The PCO executes its mission by supporting five key EA Mission Thrust Areas (Figure 2-1). The following section contains examples of PCO activities supporting each of the five EA Mission Thrust Areas.

Photo credit (opposite page): Gertrud Zach/U.S. Army

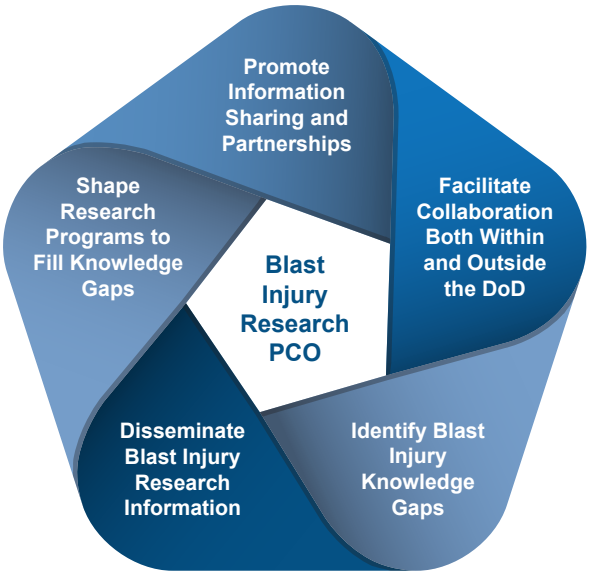


FIGURE 2-1: PCO Support of EA Mission Thrust Areas

Facilitate Collaboration within and outside of the DoD

The PCO promotes collaboration on blast injury research topics by actively engaging stakeholders within the DoD and across federal agencies, academia, and industry—both within and outside of the U.S.

Notable international collaborations include:

- The PCO Director chairs the ongoing work toward NATO HFM-270 (RTG), "Framework for Modeling and Simulation of Human Lethality, Injury, and Impairment from Blast-related Threats," and chaired the successful closure of NATO HFM-234 (RTG) "Environmental Toxicology of Blast Exposures: Injury Metrics, Modeling, Methods, and Standards."
- The PCO leads a U.S.-India research project under the Defense Trade and Technology Initiative (DTTI), an international partnership organized by the Under Secretary of Defense for Acquisition, Technology, and Logistics (USD(AT&L)) and the Indian Ministry of Defence, Defence Research and Development Organization (DRDO). encourages collaboration on experimental and computational studies of blast injury and TBI.
- The PCO established a collaboration with the National Defense Medical College of the Japan Self-Defense Forces via the Japan-U.S. Technical Information Exchange Forum on Blast Injury (JUFBI). In FY18, both sides agreed to open the forum to all interested nations and hence changed the meeting's moniker to International Forum on Blast Injury Countermeasures (IFBIC). Through this forum, the PCO encourages information sharing on research opportunities that lead to improvements in prevention, clinical diagnosis, and treatment of blast-related brain, lung, and auditory injuries.
- The PCO is active in the U.S.-Republic of Korea Technical Cooperation Sub-Committee Medical Working Group which meets to discuss various military medical research topics, and in FY18 briefed stakeholders of the efforts to make historical blast injury research data available and on computational modeling of blast injury. The overall goal for this program is to develop and validate a multiscale simulation framework for modeling blast injury.

See Chapter 3 for additional information on the PCO's international collaborations.

Notable interactions with U.S. partners include:

- The PCO Director, along with representatives from Joint Trauma Analysis and Prevention of Injury in Combat (JTAPIC), discussed opportunities to use artificial intelligence (AI) in support of PCO initiatives in computational modeling of the human effects of blast exposure with investigators from Massachusetts Institute of Technology (MIT) Lincoln Labs.
- The Blast Injury Research Program Coordinator participated in the Trauma Infections Research Program Ninth Annual Investigators Meeting where investigators presented research updates on studies involving the diagnosis of invasive fungal

wound infection (IFI), epidemiological assessment of combat-related IFIs, trauma-associated osteomyelitis, and multidrug-resistant and virulent organisms in trauma infections.

- The PCO staff continue to work with representatives from the U.S. Army Medical Research and Materiel Command (USAMRMC) and U.S. Army Research Laboratory Survivability/Lethality Analysis Directorate (ARL/SLAD) to finalize the concept of operations for a collaborative effort, the Center for Human Injury and Performance (CHIP). CHIP drives research to fill knowledge gaps in human injury and performance, drawing on expertise from the medical and nonmedical research communities, and will facilitate distribution of blast-related research data to those communities. Some of the initial efforts from CHIP will focus on knowledge gaps in blast injury, such as behind-helmet blunt trauma.
- The PCO hosted a meeting between representatives from USAMRMC directorates and subordinate commands and representatives from the Homeland Defense and Security Information Analysis Center (HDIAC). HDIAC representatives presented an overview of their capabilities and participants discussed opportunities to collaborate with HDIAC on future projects.
- The PCO Director contributed to an Inter-Agency Explosive Terrorism Risk Assessment Working Group (IExTRAWG) meeting at which progress on a tool that uses information from the intelligence community and law enforcement to characterize threats and to inform responses, was evaluated. Through this forum, the PCO stimulates information sharing on research opportunities that lead to improvements in prevention, clinical diagnosis, and treatment of blast-related brain, lung, and auditory injuries.

Identify Blast Injury Knowledge Gaps

A solid foundation of the current state of the science on blast injury is essential to the PCO's goals of identifying knowledge gaps, supporting current research efforts, and determining the appropriate direction of future work. Toward these goals, the PCO has reviewed information via scientific publication, requested information via public solicitation, and taken an active role in applying the Blast Injury Prevention Standards Recommendations (BIPSR) Process to understanding blast injury prevention standards.

Informing USAMRMC on Wearable Blast Sensors Capabilities

The PCO issued a public Request for Information (RFI) to gather information about wearable sensors available for DoD use to record acute and chronic environmental blast exposures across training environments. Information was sought on commercially available sensors in advanced development and at Technology Readiness Level (TRL) of six or higher. The PCO analyzed the responses and wrote an information paper used to inform USAMRMC's Environmental Sensors in Training (ESiT) program, recommending appropriate metrics for evaluation and determining how the respondents compare along these metrics.

Applying the BIPSR Process to Assess Candidate MHS Blast Injury Prevention Standards

In FY18, the PCO further refined the BIPSR Process, with the goal of effective and efficient identification of gaps in available candidate Military Health System (MHS) Blast Injury Prevention Standards; this Process directly supports the key EA responsibility to recommend standards for Assistant Secretary of Defense for Health Affairs (ASD(HA)) approval and DoD use. The BIPSR Process is implemented by the PCO with the assistance of the MITRE Corporation, a DoD trusted

agent that operates Federally Funded Research and Development Centers (FFRDCs). The purpose of the BIPSR Process is to identify and meticulously evaluate the details of current blast injury prevention standards to determine their suitability for use by the DoD in health hazard and survivability assessments, as well as protection system development. In FY18, assessment and rating of Auditory and Dermal Burns Blast Injury Types was initiated. In addition, the PCO continues to support the Interactive Blast Injury Prevention Standards Recommendation (iBIPSR) capability, a web-based collaboration environment, aiming to improve information sharing among blast injury experts and to provide a platform for ongoing collaboration throughout the BIPSR Process. The PCO and MITRE team are proving out the iBIPSR capability using the Auditory Blast Injury Type as an exemplar. To meet the current needs of the operational environment and DoD, the PCO has reprioritized the remaining MHS BIPSR Process Blast Injury Types. For more information on the FY18 BIPSR Process activities, see Chapter 4.

Disseminate Blast Injury Research Information

Proper dissemination of blast injury research information ensures that all stakeholders along the Research, Development, Testing, & Evaluation (RDT&E) continuum, from laboratory to field, are equipped with cutting-edge information. Dissemination of this information occurs through multiple channels, including formal reporting mechanisms, direct requests for information (RFI) to the PCO, the PCO website, and stakeholder community briefings.

Annual Report to the EA

The PCO prepares an annual report to the EA covering science and technology (S&T) efforts and programs focused on the prevention, mitigation, and treatment of blast injuries. Intended to inform senior DoD policymakers, researchers, and public audiences, the Annual Report to the EA highlights blast injury research accomplishments across the DoD within the fiscal year that address the full spectrum of blast injuries. Previous annual reports are available on the PCO website (https://blastinjuryresearch.amedd.army.mil).

Peer-reviewed Article in *Brain Injury* Detailing Challenges of Modeling Military Traumatic Brain Injury

The PCO Director, among other authors, published a peer-reviewed article in *Brain Injury* entitled, "Preclinical modelling of militarily relevant traumatic brain injuries: Challenges and recommendations for future directions" (*Cernak et al., 2017*). The article emphasized the need to accurately characterize Service member blast exposures, including exposures to repeated occupational levels of blast overpressure during weapons training, and the importance of creating relevant blast exposures in the laboratory to support blast-related brain injury research.

Preservation and Dissemination of DoD Historical Blast Bioeffects Research Data

The PCO initiated and leads the effort of preservation and dissemination of DoD historical blast bioeffects research data collected at the Albuquerque Blast Test Site on Kirtland Air Force Base (AFB), New Mexico, from 1951 to 1998. The purpose of this effort is to provide broad access to the considerable wealth of DoD historical data and findings on the biological effects of blast so that program managers, researchers, and medical decision makers can solve current and future problems with minimum duplication and maximum efficiency.

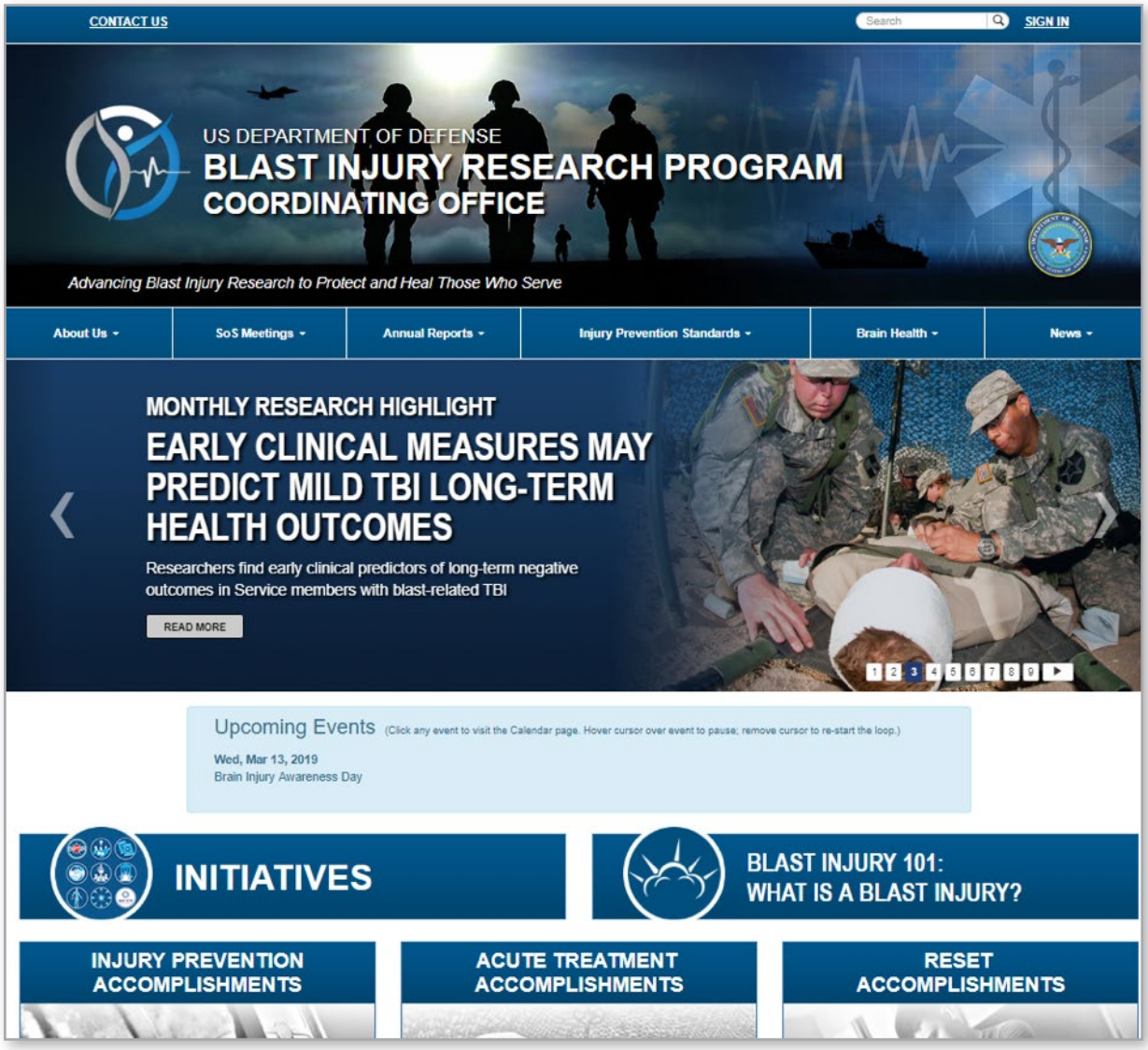
This effort supports the EA's responsibility to disseminate information so that research

programs can leverage historical knowledge and plan future research investment to address remaining knowledge gaps and avoid unnecessary and duplicative work. For more information on this project, see Chapter 6.

Web-based Blast Injury Research Information

The PCO hosts a dynamic public-facing website as a resource for information about DoD blast injury research. The website was completely redesigned in August through September 2016 and launched October 2016 as a fully responsive, disability-accessible site that can be easily viewed on mobile phones and tablets. The website, https://blastinjuryresearch.amedd.army.mil (Figure 2-2), incorporates current content that accurately reflects ongoing developments and achievements of DoD blast injury research. In FY18, the PCO updated the site monthly with timely and relevant DoD/VA-sponsored blast injury research publications, managed a calendar of blast injury-related events of interest, announced the SoS meeting and facilitated online registration, and promoted the DoD's Brain Injury Awareness Month campaign with a calendar of events and links to brain injury research partners. The website also serves as

FIGURE 2-2: Screenshot of PCO Website Home Page



a repository of blast-related information and PCO-generated content, such as the annual EA Reports and the historical SoS meeting proceedings. The EA Reports and SoS meeting proceedings continue to be the most-downloaded PDFs from the website.

As a web-based tool for stakeholders to discover opportunities to collaborate or participate in blast-related research, the PCO gathers responses and data submitted in response to blast-related RFIs, meant to direct and to inform DoD initiatives. FY18 examples of the website's collaboration capability include: collecting information and data from the research community on existing computational models for blast injury to inform the HFM-270 effort discussed in detail in Chapter 3, and data gathering of existing standards for auditory blast injury to inform the BIPSR process (Chapter 4). Also, in FY18, the PCO received inquiries through the website portal from scientists interested in research opportunities and from blast-injured warfighters interested in knowing how they could further help blast injury research.

Additionally, the PCO website acts to promote, to facilitate registration, and to provide schedule information for meetings and conferences sponsored by the PCO or by blast injury research organizations to include the International SoS meetings and the annual Military Health System Research Symposium (MHSRS).

Shape Research Programs to Fill Knowledge Gaps

The PCO helps to shape blast injury research programs by participating in research program planning, management, and advisory committees. Being an active participant in the blast injury research community ensures that key blast injury knowledge gaps are addressed, encourages collaborative research efforts, and identifies potentially duplicative research.

Shaping Research through JPCs

The PCO's continued collaboration with the Joint Program Committees (JPCs) ensures that high priority blast injury research issues are addressed in future medical research investments. In FY18, the PCO brought perspectives gained from it's research collaboration function to business meetings, In-Progress Reviews (IPRs), Review & Analysis (R&A) meetings, stakeholder meetings, and integrated product team (IPT) meetings for the Military Infectious Diseases Research Program (MIDRP, JPC-2), Clinical and Rehabilitative Medicine Research Program (CRMRP, JPC-8), Military Operational Medicine Research Program (MOMRP, JPC-5), and Combat Casualty Care Research Program (CCCRP, JPC-6). These meetings provide a high-level summary of the key areas of each program's medical research investment and highlighted the importance of DoD/VA coordination and collaboration with researchers from other federal agencies, academia, and industry. They also underscore the remaining knowledge gaps, requirements, and challenges facing each research area.

Promote Information Sharing and Partnership

Given the complex nature of blast injury, information sharing and partnerships are critical to advancing blast injury RDT&E through coordinated efforts across stakeholder communities. In FY18, the PCO participated in several activities to promote information sharing and strengthen partnerships with key national and international organizations.

Of note, PCO leadership were invited lecturers at various forums including the Annual Society for Brain Mapping and Therapeutics (Los Angeles, CA), the Society of Photographic Instrumentation Engineers (SPIE) Defense and Commercial Sensing meeting (Orlando, FL), the Medical Effects of Ionizing Radiation course (Naval Hospital Okinawa and Camp

Zama, Japan), 25th Annual Appalachian Spring Conference (Johnson City, TN), the Annual Networking and Research Update Event "Care Across the Continuum, from Point-of-Injury to Recovery," sponsored by the Centre for Blast Injury Studies Imperial College of London, and the 4th Asian Conference on Defence Technology (Tokyo, Japan).

International State-of-the-Science Meeting Series

Since 2009, the International State-of-the-Science (SoS) Meeting series continues to be a valuable forum for knowledge sharing, collaboration, and communication across blast injury research communities. In FY18, the PCO, with support from the RAND Corporation, hosted the Seventh International State-of-the-Science Meeting on "The Neurological Effects of Repeated Exposure to Military Occupational Blast: Implications for Prevention and Health." International subject matter experts (SMEs) from government organizations, academia, and industry gathered to summarize the collective knowledge on the impact of repeated exposure to military occupational blast on the brain, and to identify actionable research gaps. The evidence for this particular topic is notably sparse, despite the potential short- and long-term effects such low-level, subconcussive blast events can have on Service members.

DoD Brain Health Research Program Coordinator

The PCO's DoD Brain Health Research Program Coordinator (Coordinator) supports brain health responsibilities of the EA relevant to neurological and neuropsychological health. In FY18, the Coordinator engaged in and directed several coordinating activities to support the EA's responsibilities to disseminate brain health research and clinical practice information, facilitate collaboration, and promote information sharing among scientists and clinicians within the DoD, other federal agencies, academia and industry, both within and outside of the U.S.

Neuroscience, Neurotrauma, and Neurodegeneration Working Group

During FY18, the Coordinator took an innovative step to help the diverse community of USAMRMC brain health experts work in concert, with the creation of the Neuroscience, Neurotrauma, and Neurodegeneration Working Group (N3WG). The N3WG is chaired by the Coordinator and consists of representatives from the Congressionally Directed Medical Research Program (CDMRP), Military Operational Medicine Research Program (MOMRP, JPC-5), Combat Casualty Care Research Program (CCCRP, JPC-6), Clinical and Rehabilitative Medicine Research Program (CRMRP, JPC-8), Joint Trauma Analysis and Prevention of Injury in Combat (JTAPIC) Office, Principal Assistant for Acquisition (PAA) Office, Principal Assistant for Research and Technology (PAR&T) Office, and U.S. Army Medical Material Development Activity (USAMMDA).

The N3WG is a forum for communication and coordination among the many organizations within USAMRMC that are responsible for programmatic oversight and execution of efforts related to neuroscience, neurotrauma, and neurodegeneration. N3WG allows those organizations to leverage other's expertise in responding to external queries and needs, to generate consensus recommendations for the USAMRMC, and to speak with a single corporate voice for the USAMRMC neurobiology community. In FY18, the N3WG fielded over fifty taskers in support of those efforts.

Expert Panels and SoS Meetings

To support the PCO's mission to identify military knowledge and research gaps in brain health, the Coordinator served on several expert panels, steering committees,

Photo credit: Staff Sgt. Alex Licea/U.S. Army

and advisory boards within and outside the DoD. In FY18, the Coordinator was a member of the Scientific Advisory Board for the National Collegiate Athletic Association (NCAA)-DoD Grand Alliance: Concussion Assessment, Research, and Education (CARE) Consortium; the National Football League (NFL) Scientific Advisory Board; and the CDMRP DoD Gulf War Injury Research Program (GWIRP) FY12 Consortium Award Expert Advisory Board (EAB) face-to-face meeting. He also participated in the National Advisory Neurological Disorders and Stroke Council as the appointed DoD *ex officio* member.

In addition to serving on advisory boards, the Coordinator is actively involved in the planning and implementation of the PCO-organized International SoS Meeting series. Following each meeting, he ensures that brain health-related recommendations are shared among researchers, clinicians, policy makers, and senior leaders in and outside of the DoD to facilitate the translation of findings into tangible results that advance treatment of traumatic brain injury (TBI), blast, and neurodegenerative diseases.

Participation in these panels enables the Coordinator to identify knowledge and research gaps pertinent to brain health, and provide recommendations for research efforts and clinical practices to address identified gaps.

Research Coordination

The Coordinator supports the EA's responsibility to align DoD TBI research with the National Research Action Plan (NRAP) through participation in coordinating efforts of several large brain health related research studies. A notable example is his role as a co-Primary Investigator for the Chronic Effects of Neurotrauma Consortium (CENC), a $70 million consortium organized in support of NRAP requirements. In FY18, the Coordinator presented at a meeting sponsored by the General Electric (GE)-NFL Head Health Challenge, a

collaborative effort between the NFL, GE, and Under Armor apparel to expedite diagnosis and treatment of mild TBI (mTBI) by providing clinicians with a better understanding of brain injury and the methods to treat and mitigate damage. The Coordinator was also a panelist in the second annual conference of the NCAA-DoD Grand Alliance, sponsored by the United States Military Academy; his panel session focused on differences and similarities in return-to-activity among cadets, cadets who are NCAA athletes, and NCAA athletes.

Collaborative Research and Clinical Efforts

Through numerous brain health-related research and clinical engagements, the Coordinator promotes collaboration among researchers and clinicians from various federal government agencies, academia, and industry. To keep abreast of cutting edge research and developments in the neurotrauma investigative space, the Coordinator participated in several impactful brain health-related meetings including the Trauma Infections Research Program Ninth Annual Investigators Meeting and the 2018 Sports Concussion Conference of the American Academy of Neurology. These meetings provide a way to build and bolster relationships with researchers and clinicians from other federal government agencies, academic institutions, and industry organizations.

International Research Collaboration

To continue to facilitate collaboration within the neurotrauma research community, the Coordinator is actively involved in international research meetings. For example, from August 11-16, 2018, the Coordinator participated in the International and National Neurotrauma Societies in Toronto, Canada, at which the most up-to-date science on brain and spinal cord trauma was shared; the Coordinator presented a poster on ENIGMA: Enhancing Neuroimaging Genetics through Meta-Analysis. He also attended the 6th Annual Meeting of International Initiative for Traumatic Brain Injury Research (InTBIR) at National Institutes of Health (NIH), where presenters highlighted challenges with large data sets and discussed neuroimaging as a biomarker for TBI. Participation in these international research meetings support the EA's responsibility mandated in Public Law 109-163 to collaborate with other countries to tackle significant blast injury issues important to the DoD.

MHSRS Tract on Closing Blast Injury Research Knowledge Gaps

In support of the PCO's goals of sharing information and facilitating collaboration, the PCO sponsored a tract at the 2018 Military Health System Research Symposium (MHSRS; Kissimmee, FL) titled "Advancing Blast Injury Research to Close Critical Knowledge Gaps." Substantial preparatory work and on-site support was necessary to facilitate such an effort. The tract featured dedicated poster topics and heavily-attended breakout sessions on "Blast-Induced Tinnitus," "Minimizing the Impact of Wound Infections Following Blast-Related Injuries," "Does Repeated Blast-Related Trauma Contribute to the Development of Chronic Traumatic Encephalopathy?" and "Environmental Blast and Impact Sensors in Training and Brain Health Sustaining."

DoD Working Group on Computational Modeling of Human Lethality, Injury, and Impairment from Blast-related Threats

As future military operations become more demanding and require sustained performance over extended periods, they will pose health risks that are currently not well understood and perhaps not anticipated. Blast-related injuries sustained by Service members have increased in occurrence and severity during Operation Enduring Freedom (OEF), Operation Iraqi Freedom (OIF), and Operation New Dawn (OND). Many of these injuries cause

permanent disabilities and reduce quality of life. Understanding and developing protective measures against these blast-related threats is of utmost importance. However, accurately predicting blast-related lethality, injury, and impairment remains challenging and is time- and cost-prohibitive. Developing a new capability to model the human body's response to blast-related threats will create an avenue for exploring and understanding these risks. This capability will make it possible to rapidly develop and assess the impact of innovative personal and combat platform occupant protection concepts in a virtual environment, accelerate the development of effective treatment strategies, and predict health outcomes and disabilities. Valid predictive models will reduce the number of expensive and time-consuming dynamic tests by identifying only the specific cases that require additional experimental verification. As our Service members encounter novel threats in future combat scenarios, this capability will allow the DoD to quickly and adeptly address those threats. Reductions in resources required for Live Fire Test and Evaluation is also an expected outcome from the development of this DoD capability.

The PCO established the DoD Working Group (WG) on Computational Modeling of Human Lethality, Injury, and Impairment from Blast-related Threats in 2017. The purpose of the WG is to shape, focus, and coordinate the DoD's computational modeling efforts to enable a new capability for modeling and simulation of human lethality, injury, and impairment from the entire spectrum of blast-related threats and environments from initial point of interaction with the blast hazard to RTD (Figure 2-3). The WG includes representatives from 34 organizations across the DoD and seven other government agencies including the National Institutes of Health (NIH), the National Science Foundation (NSF), the National Aeronautics and Space Administration (NASA), the Federal Bureau of Investigation (FBI), Department of Veterans Affairs (VA), Department of Homeland Security (DHS), and the National Highway Traffic Safety Administration (NHTSA) (Figure 2-4). As members of the WG, they have been asked to share information about

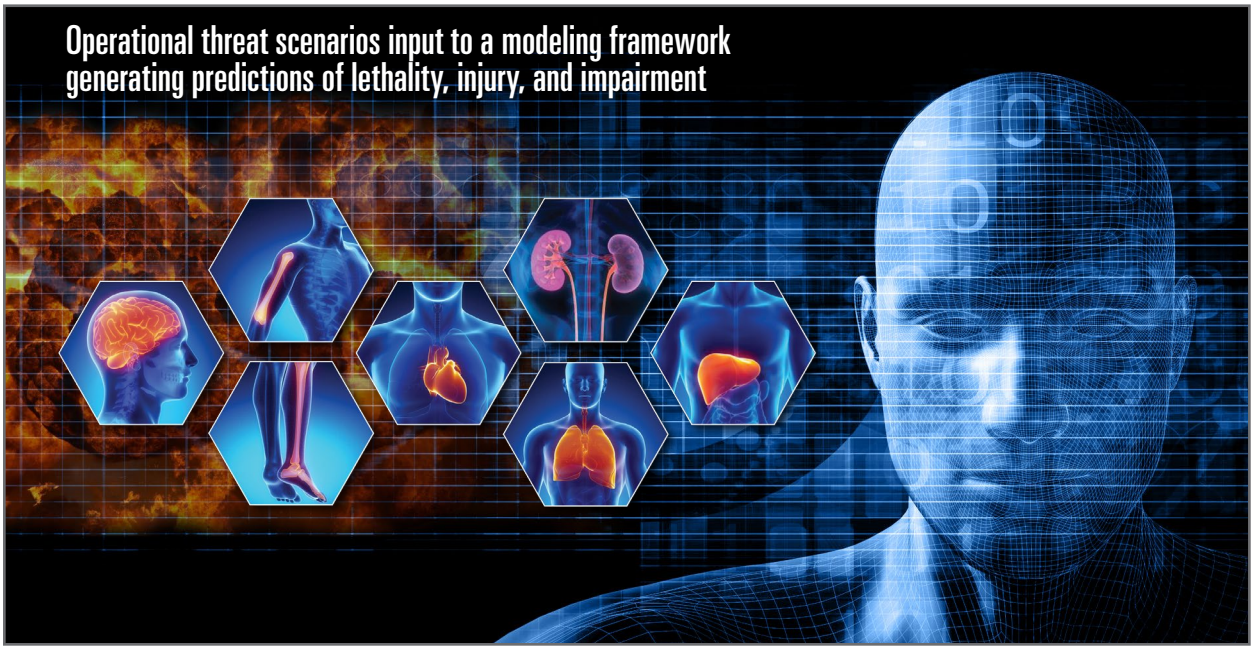


FIGURE 2-3: Desired DoD Modeling Capability Framework

FIGURE 2-4: Working Group Member Organizations

DEPARTMENT OF DEFENSE (DoD)

Office of the Assistant Secretary of Defense for Health Affairs (ASD(HA))
Office of the Assistant Secretary of Defense for Research and Engineering (ASD(R&E))
DoD Blast Injury Research Program Coordinating Office
Defense Threat Reduction Agency (DTRA)
Joint Non-Lethal Weapons Program (JNLWP)
Joint Program Executive Office-Chemical and Biodefense
Defense Health Agency (DHA)
DoD Explosives Safety Board (DDESB)
U.S. Special Operations Command (USSOCOM)

U.S. AIR FORCE

Air Force Research Laboratory (AFRL)

U.S. ARMY

Army Research Laboratory (ARL)
Military Operational Medicine Research Program (MOMRP)
Combat Casualty Care Research Program (CCCRP)
Program Executive Office (PEO) Simulation Training and Instrumentation (STRI)
Program Executive Office (PEO) Soldier
U.S. Army Corps of Engineers
U.S. Army Public Health Center (USAPHC)

U.S. NAVY

Naval Air Systems Command (NAVAIR)
Naval Medical Research Center (NMRC)
Naval Submarine Medical Research Laboratory (NSMRL)
Naval Surface Warfare Center, Carderock Division (NSWC CD)
Naval Surface Warfare Center, Indian Head Division (NSWC IHD)
Office of Naval Research (ONR)
USMC Program Executive Office (PEO) Land Systems (LS)

DEPARTMENT OF HOMELAND SECURITY (DHS)

Chemical Security Analysis Center

DEPARTMENT OF VETERANS AFFAIRS (VA)

Musculoskeletal Disorders and Medical Comorbidities Program

NATIONAL AERONAUTICS AND SPACE ADMINISTRATION (NASA)

Glenn Research Center

NATIONAL INSTITUTES OF HEALTH (NIH)

Dental and Craniofacial Research

NATIONAL SCIENCE FOUNDATION (NSF)

Mechanics of Materials & Structures Program

FEDERAL BUREAU OF INVESTIGATION (FBI)

Explosive Unit, Laboratory Division

NATIONAL HIGHWAY TRAFFIC SAFETY ADMINISTRATION (NHTSA)

Human Injury Research Division

Photo credit: Courtesy Photo/U.S. Air Force

their programs, identify opportunities for collaboration, recommend new efforts to close knowledge gaps, and develop a Strategic Plan for a computational modeling framework that will enable the Modeling Capability.

Working Group Meeting #2

The PCO hosted WG Meeting #2 on January 17-18, 2018, attended by 28 participants representing 17 DoD and six Government organizations. The MITRE team moderated the meeting, providing updates on the WG activities since the kickoff meeting. WG Members were briefed on updates to the Roadmap for the development of the Strategic Plan, the Human Body Computational Modeling Questionnaire (Modeling Questionnaire), and the Human Body Computational Modeling Registry (Modeling Registry). During the meeting, WG Members unanimously approved the Charter for staffing to the EA, reviewed and approved the Modeling Questionnaire, and unanimously approved the Roadmap.

Working Group Meeting #3

The PCO hosted WG Meeting #3 on September 12-13, 2018, where 22 participants representing 13 DoD and six other Government organizations attended. Member presentations informed the WG on best-practice approaches for consideration in the development of the Strategic Plan. The MITRE team also shared information on 55 human body computational models, provided by WG Members via the Modeling Questionnaire. This activity led to identification of potential gaps in body regions and blast injuries not currently captured by models, which may require future development to enable the complete desired modeling capability. WG Members unanimously approved inviting performers to the Meeting #4 to gather information on the state of the science to inform development of the Strategic Plan. WG Members also participated in an activity to efficiently generate ideas to inform the Strategic Plan.

Next Steps

The next steps for the Working Group in the coming year include:

1. Prepare initial draft of the Strategic Plan
2. Developing a Modeling Registry prototype for Human Body Computational Models
3. Continuing collaboration with academia and industry to understand the state of the science in human body computational models used to predict human lethality, injury, and impairment from interaction with the blast hazard to return-to-routine across the taxonomy to blast-related hazards

JTAPIC Program

The JTAPIC Program supports a specific EA responsibility codified in DoDD 6025.21E. JTAPIC provides actionable analysis to DoD Stakeholders for the modification of personal protective equipment, tactics techniques and procedure, and vehicle platforms to provide decision support for the prevention and mitigation of injury. As of FY17, JTAPIC produces its own retrospective Annual Report, from which the reader can learn more about its excellent work.

The JTAPIC Program Management Office originally resided within the PCO, but it has since matured into a program of record.

The JTAPIC Program Management Office is located at Fort Detrick, Maryland, with partners throughout the U.S. (Table 2-1). It leverages the medical, intelligence, operational, and materiel expertise of these partnerships to support operational planning and the development of strategies to prevent or mitigate injuries during combat. The JTAPIC Program's key FY18 accomplishments are highlighted in Chapter 7.

TABLE 2-1: JTAPIC Program Partners

Intelligence and Operational Partners
National Ground Intelligence Center
Dismounted Incident Analysis Team
U.S. Marine Corps Current Operations Analysis Support Team
Marine Corps Intelligence Activity
U.S. Army Aeromedical Research Laboratory
Medical Partners
Armed Forces Medical Examiner System
Joint Trauma System
Naval Health Research Center
Materiel/Acquisition Partners
Project Manager, Soldier Protection Individual Equipment
Product Manager, Infantry Combat Equipment
U.S. Army Research Laboratory

Way Forward

The PCO was established by the Commander, U.S. Army Medical Command (MEDCOM), to coordinate blast injury-related research efforts on behalf of the EA in support of prevention, mitigation, and treatment solutions for Service members impacted by blast injuries. The PCO upholds the EA's Mission Thrust Areas by sharing critical information on knowledge gaps in blast injury research sourced from collaborative efforts with researchers and clinicians across domestic and global blast injury Research, Development, Testing, & Evaluation (RDT&E) and operational communities. For information on PCO activities in FY19 and beyond, see Chapter 8.

03

CHAPTER 3:

INTERNATIONAL COLLABORATIVE PROGRAM ACTIVITIES

Blast injury affects Service members and their Families worldwide and is also of significant concern to our Nation's allies and friends. As such, the PCO participates in several collaborative efforts of global scope and interest, in which the best talent and technology the world has to offer is leveraged for the protection of the Warfighter from blast injury. These activities include an ongoing participation in NATO-led efforts to direct more precisely mitigation strategies for blast injury and broad ranging collaborations with India, Japan, Republic of Korea, and others to pool scientific and technical expertise in blast injury.

NATO S&T BUSINESS MODELS

1. **Collaborative:** NATO provides a forum where NATO Nations and partner Nations elect to use national resources to define, conduct, and promote cooperative research and information exchange.
2. **In-house delivery:** S&T activities conducted in a NATO dedicated executive body, having its own personnel, capabilities, and infrastructure.

Science and Technology at NATO

Explosive weapons are a significant and continuing source of casualties and injuries in NATO operations. Recent advances in personal protective equipment (PPE), in-theater medical care, and rapid evacuation are increasing survivability of blast encounters. Survivors of blast injuries commonly suffer from traumatic brain injury (TBI), visual and auditory system injury, and extremity injuries resulting in amputation of the limb(s). NATO advances blast injury research through Science and Technology (S&T) activities.

The Science and Technology Organization (STO) is a NATO subsidiary body established to meet the collective S&T needs of NATO Nations and partner Nations. S&T activities embrace scientific research, technology development, transition, application and field-testing, experimentation, and a range of related scientific activities that include systems engineering, operational research and analysis, synthesis, integration, and validation of knowledge derived through the scientific method. NATO conducts these activities through two business models (see inset).

The Collaboration Support Office (CSO), one of three executive bodies within the STO, provides executive and administrative support to the activities conducted within the framework of NATO's collaborative business model. The CSO consists of six Technical Panels and one Group (Table 3-1) focusing on different S&T areas. Technical Panels and Groups, which drive S&T collaborative model activities, are made up of Technical Teams (TTs) of national representatives, renowned scientists, engineers, and information specialists. In addition to providing critical technical oversight, the TTs provide a communication link to military users and other NATO bodies. The TTs conduct specific research activities of defined duration and format including task groups, workshops, symposia, specialists' meetings, lecture series, and technical courses.

TABLE 3-1: Six CSO Technical Panels and One Group

Collaboration Support Office	
Acronym	**Name**
AVT	Applied Vehicle Technology Panel
HFM	Human Factors and Medicine Panel
IST	Information Systems Technology Panel
SAS	System Analysis and Studies Panel
SCI	Systems Concepts and Integration Panel
SET	Sensors and Electronics Technology Panel
NMSG	NATO Modelling and Simulation Group

Photo credit (opposite page): NATO

Photo credit: NATO

The mission of the Human Factors and Medicine (HFM) Panel, one of the six CSO Technical Panels, is to provide the scientific and technological base for optimizing health, human protection, well-being, and performance of the Service member in operational environments with consideration of affordability. This mission is accomplished by exchange of information, collaborative experiments, and shared field trials, and involves understanding and ensuring the physical, psychological, and cognitive compatibility among military personnel, technological systems, missions, and environments.

Since April 2008, the PCO has participated in several HFM Panel activities related to blast injury (inset). These activities sought to develop a greater understanding of the mechanisms of blast injury and to translate scientific discoveries into prevention, mitigation, and treatment measures. In FY18, the PCO chaired two HFM RTGs, described hereafter.

HFM-234 (RTG): Environmental Toxicology of Blast Exposures: Injury Metrics, Modeling, Methods, and Standards

In FY18 the PCO-chaired HFM-234 (RTG) was brought to a successful close on the initially-determined schedule, with the promised deliverables published or ready for publication, and poised to contribute significantly to the establishment of a common framework for blast injury research.

Established in late 2012, HFM-234 (RTG)'s objective was to establish a framework for a new interdisciplinary research area focusing on the environmental toxicology of blast exposure. Previous discussion from the HFM-207 Symposium highlighted research similarities between blast injury research and classic toxicology; both require an understanding of dose, mechanism of dose delivery, and dose-dependent endpoints. In consideration of these similarities, the purpose of the HFM-234 (RTG) has been to address knowledge gaps by creating a systematic approach to better understand blast injuries.

PREVIOUS NATO HFM ACTIVITIES RELATED TO BLAST INJURY

- HFM-090: Test Methodology for Protection of Vehicle Occupants against Anti-Vehicular Landmine Effects (2002–2006)
- HFM-175: Medically Unexplained Physical Symptoms in Military Health (2008–2012)
- HFM-193: mTBI in a Military Operational Setting (2009–2013)
- HFM-198: Injury Assessment Methods for Vehicle Active and Passive Protection Systems (2010–2013)
- HFM-207 Symposium: A Survey of Blast Injury across the Full Landscape of Military Science (2010–2012)

Objectives of the HFM-234 (RTG) were to build an evidence based outline for NATO standards for blast injury analysis; to examine opportunities for improvements in the standards of medical care for blast injury; to explore advancing the state of practice in computational modeling of blast injury in relevant operating environments; and to explore standardized animal models and toxicology research protocols that could be adopted by research and technology programs across NATO.

These focus areas were organized into five key deliverables:

- A comprehensive dictionary of blast injury terms
- Guidelines for conducting epidemiological studies of blast injury
- Guidelines for reproducing blast exposures in the laboratory
- Guidelines for using animal models in blast injury research
- Final technical report on HFM-234 activities

Comprehensive Dictionary of Blast Injury Terms

Recognizing the need for a common vocabulary of blast injury research terms to improve communication and facilitate multidisciplinary cross-community collaboration, the HFM-234 TT developed the "Comprehensive Dictionary of Blast Injury Terms" that defines 190 unique words and concepts.

Guidelines for Conducting Epidemiological Studies of Blast Injury

Blast-related injuries are notoriously difficult to survey as they have multiple causes, occur during chaotic circumstances, and take the clinical form of multiple short-term or chronic symptoms. To foster an environment conducive to collecting accurate and reproducible epidemiologic data on blast injuries, fifteen experts from nine NATO nations collaborated to develop a framework modeled after the Institute of Medicine (IOM) protocol. The guidelines identify critical elements of blast injury epidemiological studies, including:

- A well-defined research question
- A focused hypothesis
- A well-defined research plan
- Sampling methods
- Identifying biases and study limitations
- Data analysis plan defining all variables and sample size requirements
- Documenting survey instruments and operational procedures
- Other considerations to include the analysis phase, banking of biological specimens, interdisciplinary approaches, quality assurance, and ethics

By standardizing data collection and analysis of epidemiological studies of blast injury, these guidelines will improve the ability of international partners to share data, compare outcomes, and collaborate on future multinational studies.

Guidelines for Reproducing Blast Exposures in the Laboratory

The HFM-234 (RTG) noted that the experimental blast injury literature contained considerable variability in methodologies, approaches, and end-points that were difficult to compare across studies. Along with incomplete reporting and researcher inexperience, these inconsistencies limited generalizability to other scenarios outside of the laboratory.

This HFM-234 (RTG) guideline recommended tailoring the blast induction methodology to the real-world operational condition of interest, but also drawing direct comparisons to alternative blast platforms to facilitate harmonization of results; any deviation from prior standards should be rationalized and thoroughly described.

Consistent use of the proposed guidelines will allow for reliable comparisons to be made between studies with different laboratory settings, methods of blast wave generation, and type of measured blast injuries.

Guidelines for Using Animal Models in Blast Injury Research

The guidelines for using animal models in blast research provide a framework for scientifically valid methods to address the pathological consequences of blast exposures and assist researchers during all stages of preclinical blast experiments. It is anticipated that this will reduce inter-laboratory variability and allow valid comparison of results. These recommendations are not intended to be overly prescriptive, but designed to ensure experimental validation and replication of the human condition to better translate the results to military treatment facilities.

Outcomes from HFM-234 (RTG)

The five deliverables were finalized at the last HFM-234 (RTG) meeting in January 2016 at Porton Down, Wiltshire in the UK. The key deliverables were reviewed and approved by the nine participating nations.

The full final technical report for HFM-234 is now available to the public from the NATO Science and Technology Organization at https://www.sto.nato.int as Technical Report STO-TR-HFM-234. The three guidelines deliverables and an associated editorial were published in the *Journal of the Royal Army Medical Corps* in FY18:

- Bieler D, Cernak I, Martineau L, et al., Guidelines for conducting epidemiological studies of blast injury. *Journal of the Royal Army Medical Corps*. 2018
- Josey T, Ouellet S, Bieler D, et al., Guidelines for reproducing blast exposures in the laboratory. *Journal of the Royal Army Medical Corps*. 2018
- Watts S, Kirkman E, Bieler D, et al., Guidelines for using animal models in blast injury research. *Journal of the Royal Army Medical Corps*. 2018
- Leggieri MJ, Jr., Bieler D, Bjarnason S, et al., Environmental toxicology of blast exposures: injury metrics, modelling, methods and standards. *Journal of the Royal Army Medical Corps*. 2018

Advancements in blast injury prevention and treatment for Service members require close collaboration between researchers, clinicians, engineers, and other stakeholders both domestic and internationally. By developing official NATO documents to standardize how data are collected, coded, and analyzed, the HFM-234 (RTG) continues to lift the barriers to cross-study comparison with the publication of the guidelines for conducting epidemiological studies of blast injury, dictionary of blast injury terms, guidelines for reproducing blast exposures in the laboratory, and guidelines for using animal models in blast injury research.

Photo credit: NATO

HFM-270 (RTG): Framework for Modeling and Simulation of Human Lethality, Injury, and Impairment from Blast-related Threats

The HFM-207 Symposium highlighted requirements for biomedically-valid computational models and simulation of blast injury that incorporate both biomechanical and physiological responses. The PCO proposed a new RTG leveraging previous, ongoing, and planned blast injury biomedical research and computational modeling efforts among the participating Nations. This HFM RTG proposal was approved by the NATO STO in late 2015 and was designated HFM-270 (RTG) with the kickoff meeting conducted in October 2016 and culminating with the final report in 2019.

The objective of this RTG is to develop a conceptualized Framework with component computational models that is capable of providing threat-to-outcome modeling and simulation (M&S) of human lethality, injury, and impairment in all blast threat environments.

TABLE 3-2: HFM-270 (RTG) Topics

The HFM-270 (RTG) will develop the framework for creating and evaluating effective systems that protect Service members from blast-related threats. The topics to be covered include the following:

- Computational modeling of human lethality, injury, and impairment from blast threats, in both mounted and dismounted scenarios
- Previous, ongoing, and planned blast injury biomedical research and computational modeling efforts, and how these fit into overarching frameworks for understanding mechanisms of injury and development of protective systems
- Identification of the gaps that remain in the mechanisms of blast-related injury and in understanding how to adequately protect from these injuries
- Survey of blast lethality, injury, and impairment research infrastructure and identification of cross-NATO research opportunities

The M&S capability that will be enabled by the Framework will make it possible to respond to anticipated and emerging blast threats by rapidly developing and testing novel blast protection concepts in a virtual environment. This capability could dramatically reduce the time and cost required to develop, build, and live-fire test prototype blast injury protection systems, and accelerate the delivery of effective blast protective equipment to Service members. Table 3-2 describes the topics that are covered by HFM-270 (RTG).

The PCO Director continues to chair this RTG of subject matter experts (SMEs) from the U.S., Canada, France, Germany, Israel, The Netherlands, Sweden, Turkey, South Africa, and the United Kingdom (Figure 3-1). The Program of Work (PoW) was finalized in early FY17 at the kickoff meeting (Table 3-3).

The PoW consists of regularly scheduled meetings that will be hosted by a different participating Nation. The purpose of each meeting is to scope the breadth of the existing computational models and modeling capabilities; assess these models and capabilities using assessment criteria for inclusion in the Framework; identify gaps in the Framework; and develop key products outlined below. Participating scientists, clinicians, and engineers from the international, military, academic, and industrial communities will present their existing computational models and modeling capabilities.

FIGURE 3-1: HFM-270 (RTG) Participating Nations

NATO OTAN

UNITED STATES

Mr. Michael Leggieri, Chair
Dr. Raj Gupta, Executive Secretary
U.S. Army Medical Research and Materiel Command

Dr. Amit Bagchi
Naval Research Center, Washington DC

Dr. Ibolja Cernak
University of Alberta Edmonton, AB

CANADA

Dr. Amal Bouamoul
Defence Research and Development Canada, Valcartier

Dr. Thomas Sawyer
Defence Research and Development Canada, Suffield

Mr. Tyson Josey
Defence Research and Development Canada, Suffield

FRANCE

Dr. Philippe May
Armed Forces Biomedical Research Institute

GERMANY

Dr. Dan Bieler and Dr. Axel Franke
German Armed Forces Central Hospital, Koblenz

ISRAEL

Dr. Tomer Erlich, and Dr. Avraham Yitzhak
Trauma and Combat Medicine, Tel Aviv

THE NETHERLANDS

Mr. Mathieu Philippens
TNO Defence, Security and Safety, Rijswijk

SWEDEN

Dr. Marten Risling and Dr. Mattias Skold
Karolinska Institutet, Stockholm

TURKEY

Mr. Atil Erdik
OTOKAR

Dr. Pinar Huri
Ankara University, Ankara

Mr. Ilker Kurtoglu
FNSS Savunma Sistemleri A.Ş.

Dr. Levent Turhan
TÜBİTAK

SOUTH AFRICA

Mr. Thanyani Pandelani
Council for Scientific and Industrial Research, Pretoria

Mr. David Reinecke
Council for Scientific and Industrial Research, Pretoria

UNITED KINGDOM

Dr. Emrys Kirkman and Dr. Sarah Watts
Defence Science and Technology Laboratory

OBJECTIVE:
To develop a multiscale, multiresolution computational framework to predict human lethality, injury, impairment, and long-term health effects across the spectrum of blast-related threats and the development of personnel protective armor, injury diagnostics, combat casualty care techniques, and rehabilitation tools.

TABLE 3-3: HFM-270 (RTG) Program of Work

Activity Workshop	Month/Year	Purpose	Host/Location
Meeting 1	Oct 5–6, 2016	HFM-270 (RTG) Kick-off	STO-CSO (Paris, France)
Meeting 2	Jan 10–12, 2017	Identify Elements of the Framework	U.S. (Fort Detrick, Maryland)
Meeting 3	Jul 11–13, 2017	Scope Breadth of Existing Models	United Kingdom (Porton Down, Wiltshire)
Meeting 4	Nov 7–9, 2017	Overview of Existing Computational Models	The Netherlands (Rijswijk)
Meeting 5	Mar 6–8, 2018	Overview of Existing Computational Models	Germany (Koblenz)
Meeting 6	Jul 10–12, 2018	Apply Assessment Criteria to Existing Computational Models	Canada (Suffield Research Center, Alberta)
Meeting 7	Dec 3–7, 2018	Finalize the Framework and Develop Blast Scenarios	South Africa (Stellenbosch)
Meeting 8	Apr 2–5, 2019	Review Demonstration Results, Identify Gaps and Finalize Dictionary, Technical Activity Proposal, and Manuscripts	Sweden (Stockholm)
Meeting 9	Sep 3–6, 2019	Finalize All Deliverables	STO-CSO (Paris, France)

The purpose of the HFM-270 (RTG) is to develop six key products:

- Framework for computational models of human lethality, injury, and impairment from blast threats, in both mounted and dismounted scenarios in any threat environment
- Dynamic repository of existing modeling capabilities
- Comprehensive dictionary of modeling and simulation terms
- Draft technical activity proposal for new HFM RTG which would develop a standardization and validation criteria for the Framework
- Publications in appropriate peer-reviewed journals
- Final report with Framework, gaps, and recommendations (2019)

In FY18, the HFM-270 (RTG) TT members participated in three in-person meetings. At the November 2018 meeting in Rijswijk, The Netherlands, the TT members were briefed by Dutch SMEs on computational modeling of blast injury research being conducted at The Netherlands Organisation for Applied Scientific Research. The TT members from each participating Nation presented responses from colleagues to the questionnaire finalized at the previous meeting which summarized existing computational models and modeling capabilities related to blast injury research. The TT finalized the plan to conduct a systematic literature review that will focus on all published computational models related to blast exposure and include both medical and nonmedical literature from 1980 to September 2017.

In March 2018, the HFM-270 (RTG) TT members assembled in Koblenz, Germany and continued to review the computational models and modeling capabilities collected by each of the participating Nations. TT members reviewed the action items from the previous meetings and then went through a practical exercise to apply the screening tool assessment to a candidate computational model

to determine its feasibility for inclusion in the Framework.

Five physicians from the German Federal Armed Forces and the DoD Brain Health Research Program Coordinator gave a series of presentations on the clinical outcomes that need to be achieved in computational modeling of blast injuries from a clinician's perspective. The TT members broke into working groups to continue to update the Comprehensive Dictionary of Blast Injury Terms developed by the HFM-234 (RTG); to conduct a systematic literature review; and to prepare a follow-on technical activity proposal.

In July 2018, the HFM-270 (RTG) TT members gathered in Medicine Hat, Alberta, Canada. They conducted a practical exercise to apply the screening tool assessment finalized at the March 2018 meeting to a candidate computational model to determine its feasibility for inclusion in the Framework. Several SMEs from the Defence Research and Development Canada Suffield Research Centre gave a series of presentations on computational models being used in ongoing blast-related research. The meeting concluded with an in-depth discussion of next steps in developing the computational modeling Framework, creating an example scenario, and the outline for the final technical report.

The next HFM-270 (RTG) meeting is scheduled for December 2018 and will be hosted by the South African TT members in Stellenbosch, Cape Provence, South Africa.

U.S.-India Collaboration on Experimental and Computational Studies of Blast and Blunt TBI

The PCO continues to be a key player in the Defense Trade and Technology Initiative (DTTI), an international partnership organized by the USD(AT&L) and the Indian Ministry of Defence, Defence Research and Development Organization (DRDO). Under the U.S.-India DTTI, the PCO and MOMRP initiated a project titled, "Experimental and Computational Studies of Blast and Blunt Traumatic Brain Injury." The lead collaborative organizations are the USAMRMC and the Institute of Nuclear Medicine and Allied Sciences (INMAS)-DRDO, Ministry of Defence, India. Other participants include the Biotechnology High Performance Computing Software Applications Institute (BHSAI), New Jersey Institute of Technology (NJIT), Walter Reed Army Institute of Research (WRAIR), Naval Research Laboratory (NRL), U.S. Army Research Laboratory (ARL), Indian Defence Institute of Psychological Research (DIPR), and Indian Terminal Ballistics Research Laboratory (ITBRL). Project objectives include:

- Develop and validate a blast injury animal model for mTBI using imaging techniques and histological procedures, as well as assessing changes in behavior and cognition
- Develop, validate, and cross-validate a computational model for blast and blunt injury
- Develop anatomically accurate head/brain models for blast/brain injuries from clinical and experimental data
- Compare the blunt and blast data to develop a scaling ratio

The objective of this project is to create blast injury animal models of mTBI to help elucidate the mechanisms of injury. Validated computational/anatomical models can expedite identification, selection, and transition of prevention and treatment strategies to clinical trials. Validated animal models to improve the design of PPE could be translated to commercial defense industry. The injury severity scale for blast-induced mTBI could be used to inform MHS clinical practices in theater and during treatment.

During FY18, there were two Project Steering Committee Meetings and Training Workshops at which the research progress was reviewed and evaluated. The first of these was held at NJIT in Newark, NJ from October 2–4, 2017. During the meeting, collaborating investigators from both

Photo credit: NATO

U.S. and India shared their research progress and discussed topics such as the standardization of shock tube configurations across research sites; establishment of a master dose-response curve; a computational model of the rat brain with cerebral vasculature; creation of a survival curves for blast and blunt head injury; and collection and analysis of magnetic resonance imaging (MRI) data from human blunt impact TBI patients. The meeting concluded with a discussion of sharing research data, more frequent project participant meetings, use of common data elements, plan for collecting and analyzing experimental data, and development of a detailed project plan for the next year of the collaborative project.

The second project meeting occurred from April 2–6, 2018 at INMAS in New Delhi. At this meeting each participating group gave a detailed task-by-task update of progress since the last project meeting. Breakout sessions were held for intergroup interactions, and a hands-on workshop was conducted jointly by American and Indian team members. INMAS gave a tour of some of their lab facilities, including their shock tube facility for blast simulation and their neurobehavioral suite and MRI labs. Researchers from both countries took advantage of the opportunity to conduct joint experiments.

A related meeting occurred from August 13–14, 2018, when the PCO Deputy Director and the USAMRMC Principal Assistant for Research and Technology participated in the U.S.-India Joint Technology Group (JTG) #20 Meeting in Bangalore, India. The JTG is a subgroup to the Defense Policy group and provides a forum for discussion and coordination of defense research and production matters. The U.S. and India have created a wide range of strategic

partnerships that reflect their common principles and long-term strategic convergence of shared national interests. During the meeting, several ongoing project agreements were briefed including the accomplishments and progress of the U.S.-India collaboration on experimental and computational studies of blast injury and TBI. U.S.-India JTG co-chairs supported the request from both India and U.S. project leads for an extension of the Project Agreement and asked to initiate the staffing of the extension. Defense and security cooperation are a key component of the bilateral relationship between India and the U.S., and JTG has evolved to become a vital pillar of engagement between the two countries.

International Forum on Blast Injury Countermeasures

The PCO has been collaborating with the National Defense Medical College (NDMC) of the Japan Self-Defense Forces (JSDF) since 2016 via the Japan-U.S. Technical Information Exchange Forum on Blast Injury (JUFBI). JUFBI brought together the PCO, NDMC, the Tokyo University of Agriculture and Technology, USAMRMC, and RDECOM in two productive discussions in 2016 and 2017. The purpose of these Forums was to bring together blast injury researchers and clinicians from the U.S. and Japan to share expertise, experience, and endeavors for solving blast injury problems of mutual interest; for identifying knowledge gaps; and for encouraging collaborative research opportunities that lead to improvements in prevention, clinical diagnosis, and treatment of blast-related brain, lung, and auditory injuries.

These meetings have produced greater information exchange between the PCO and Japanese blast research efforts in FY18. For example, from November 29–December 1, 2017, the PCO Deputy Director presented a keynote address, "Scope of Blast Injuries" and a tutorial on "The State-of-the-Art in Blast-Induced Brain Injury," and co-chaired a session on blast injuries, at the Fourth Asian Conference on Defence Technology in Tokyo. JUFBI culminated this year with three consecutive blast injury research information exchange meetings in Tokyo, attended by the PCO Director and Deputy Director. The PCO organized these meetings in coordination with the NDMC, the U.S. Army Research, Development and Engineering Command International Technology Center-Pacific (RDECOM ITC-PAC), and the Japan Ministry of Defense (JMoD) Acquisition, Technology and Logistics Agency (ATLA). The first U.S.-Japan Service to Service (S2S) (Medical) meeting was held under the auspices of the Office of the Deputy Assistant Secretary of the Army for Defense Exports and Cooperation (DASA(DEC)) on May 7, 2018 to bring together USAMRMC research program directors and their JSDF counterparts to identify topics of mutual interest that could be targets for future information exchanges and collaborative research. Several potential topics of collaboration were identified and the PCO is facilitating follow-on discussions between American and Japanese SMEs to develop a final list of potential topics that can be presented at the next U.S.-Japan Army/Ground S2S Dialog meeting. JUFBI-2018 was held on May 9–11, 2018 with international experts from diverse medical and engineering disciplines. Experts exchanged ideas on a range of blast injury topics, including traumatic brain injury, auditory injury, and wound infections. The U.S.-Japan Closed-door Planning Meeting was held on May 14, 2018 to discuss the draft Project Arrangement (PA) on "Blast-induced Injury Mechanisms and Model (BIMM)," common data elements, and plans for the next JUFBI. Both sides agreed that future forums should be open to all interested nations. Given this change, both sides agreed to change the name of the forum to "International Forum on Blast Injury Countermeasures (IFBIC)."

Photo credit: NATO

U.S.-Republic of Korea (ROK) Technological Cooperation Sub-Committee Medical Working Group

The PCO continues to be an active voice in the U.S.-ROK Technological Cooperation Sub-Committee Medical Working Group. This Working Group was established in 1990 under a Data Exchange Agreement. The meeting serves as a forum for the U.S. and ROK to discuss and exchange information on wide-ranging military medical research topics. At the FY18 meeting, November 2–3, 2017, in Seoul, Korea, the PCO Director presented two briefings, each highlighting a different PCO-led initiative. The first briefing focused on efforts to recover and share historical blast injury research data from USAMRMC through a web-based portal, as discussed in Chapter 6 of this Report. Data in this archive dates back to the 1950s and is an invaluable resource for establishing training safety guidelines, designing PPE, and developing injury treatments. The second briefing focused on computational modeling of blast injury. The

overall goal for this program is to develop and validate a multiscale simulation framework for modeling blast injury. The Korean participants, who were primarily ROK military clinicians, expressed interest in collaborating in both initiatives, and were particularly interested in the historical blast injury data recovery project, as it more closely aligns with their focus and expertise on treatment. The PCO continues to identify partners within the ROK military to discuss opportunities for collaboration. The PCO also plans to participate in the FY19 meeting, to be held in November 2018 at Fort Detrick, Maryland.

04

CHAPTER 4:

MHS BLAST INJURY PREVENTION STANDARDS RECOMMENDATION PROCESS

DoDD 6025.21E assigns to the Executive Agent (EA) the responsibility to "provide medical recommendations with regard to blast injury prevention, mitigation, and treatment standards to be approved by the Assistant Secretary of Defense for Health Affairs (ASD(HA))." The term "MHS Blast Injury Prevention Standard" is defined as a "biomedically-valid description of the physiologically- or biomechanically-based injury and performance response of a human to blast insults." The standards can range from simple dose-response curves and injury thresholds that address single components of blast insults, such as peak force, to complex algorithms and computational models that address multiple components of blast insults, such as force-time history. Candidate standards include injury thresholds, human injury probability curves (HIPC), and injury prediction tools needed to generate the information for informed trade-off and risk acceptance decisions by appropriate decision makers in the Research, Development, Testing, and Evaluation (RDT&E), medical, and operational Stakeholder communities across the DoD Components. These standards support weapon system Health Hazard Assessments (HHAs), combat platform occupant survivability assessments, and protection system development and performance testing (Figure 4-1).

Designed to address the above requirement, the MHS BIPSR Process is the DoD's first unbiased, inclusive, stakeholder-driven process designed to identify and assess the suitability and applicability of existing candidate standards and to recommend standards that meet DoD Stakeholder needs with a suitable level of validity, rigor, precision, and confidence.

The BIPSR Process has two major objectives. The first is to identify existing biomedically-valid candidate standards for immediate use by the DoD. The second is to inform the research community of gaps where no suitable candidate standards exist. The BIPSR Process is not a research program and does not develop new candidate standards. The BIPSR Process also does not attempt to impose acceptability or survivability requirements on the Stakeholder communities; rather, it seeks to ensure that the DoD uses the best available, scientifically sound, and biomedically-valid standards that will protect our Service members from blast injuries.

The BIPSR Process

The BIPSR Process is designed to identify and objectively evaluate the details of available blast injury prevention standards to determine their suitability for use by the DoD in health hazard and survivability assessments, as well as protection system development.

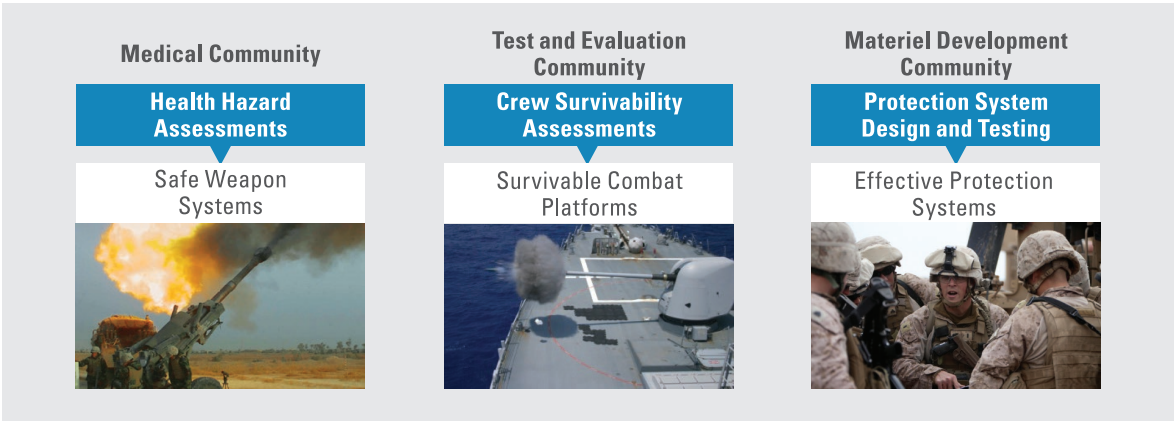


FIGURE 4-1: Blast Injury Prevention Standards Framework

Photo credit (opposite page): 2nd Lt. Sebastian Sans/U.S. Army

The BIPSR Process can be tailored for a specific mechanism of injury, resulting in an objective set of recommendations that can serve as the basis of a medical standard. Further, the Process is designed to identify and evaluate blast injury prevention candidate standards and to recommend those that would best serve as MHS Blast Injury Prevention Standards to inform the DoD medical, test and evaluation (T&E), Materiel Development, and operational communities.

Core elements of the BIPSR Process include:

- **BIPSR Process Stakeholders Committee:** Defines the problem statement and scenarios to be assessed, identifies gaps in the current standard set, drives implementation, and participates in all major decisions throughout all phases of the BIPSR Process.
  - ***Focused Stakeholder Committee:*** A subset of BIPSR Process Stakeholders with expertise related to a particular Blast Injury Type. They review existing capabilities to include a literature survey using relevant keywords, identify subject matter experts (SMEs), identify existing candidate standards, define intended uses, and identify gaps.
- **SME Panel:** A broad-based, non-advocacy panel whose members are drawn from industry, academia, and government. The SMEs have experience in the domain of interest, development of the candidate standard product (*e.g.*, dose-response curve, computational model), T&E, clinical medicine, and Independent Verification and Validation (IV&V).
- **Stakeholder Driven Consensus-Building Meeting:** A forum for Stakeholders, the SME Panel, users, analysts, and candidate standard developers to discuss the DoD's intended uses, gaining context and scope for the evaluation, and allowing for individual interviews with developers to gain a detailed understanding of candidate standard capabilities and/or profiles.

The BIPSR Process is initiated by a literature review that serves two purposes: (1) identify existing capabilities and standards pertinent to the injury under evaluation, and (2) compile a list of appropriate experts who may serve on the SME Panel that performs the evaluations. Once a list of candidate standards has been defined, the iterative nature of the BIPSR Process builds layers of information about the capabilities of each candidate under consideration.

The SME Panel conducts the initial evaluations, giving balanced, objective, and knowledgeable advice on the candidate standard's suitability for the DoD's intended uses based on the available information.

The list of candidate standards is narrowed based on an evaluation against a set of defined criteria. Information generated through the evaluation process serves as the basis for a meeting that provides a forum for Stakeholders (users, analysts, and developers) to build consensus, share information, and discuss the applicability of a candidate standard to the DoD's intended use—potentially narrowing the list of candidates that move forward in the evaluation process. In some cases, (*e.g.*, for computational models), the candidate standards undergo a detailed examination of capabilities through a rigorous test process focused on Stakeholder-defined test scenarios. Once the test cases have been run, the results are assessed using statistical tools. In the final step of the BIPSR Process, the non-advocacy SME Panel and BIPSR Process team conduct final evaluations, develop standards recommendations, and prepare process improvement recommendations.

Collaboration opportunities are integrated across the BIPSR Process. As depicted in Figure 4-2, the BIPSR Process consists of seven fundamental subprocesses represented by six pillars supporting an overarching process.

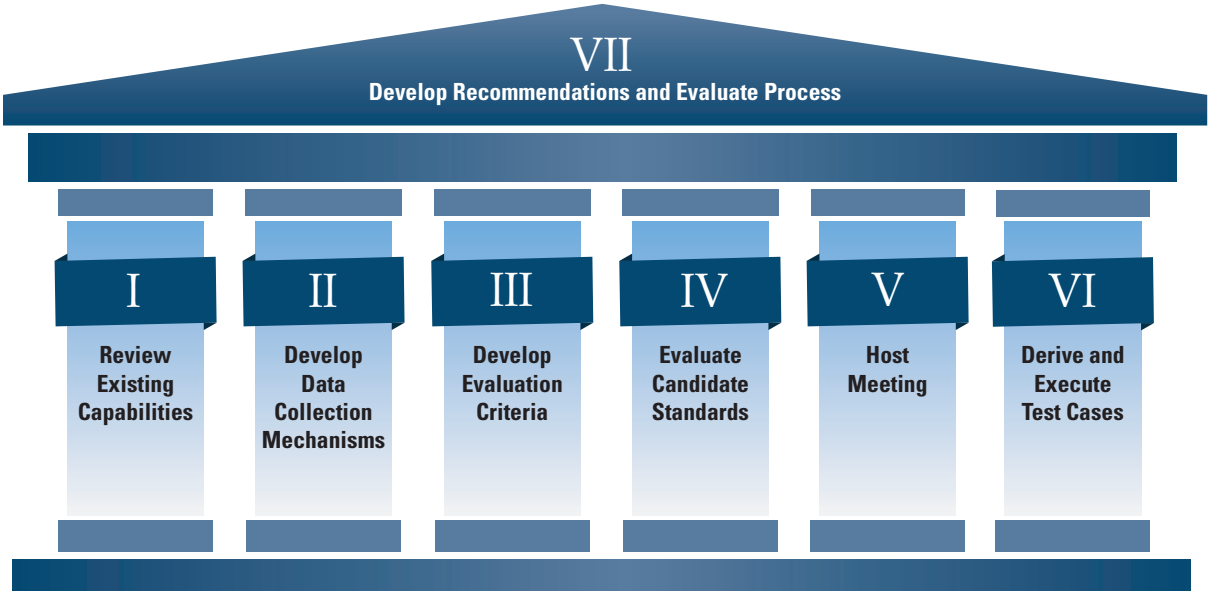


FIGURE 4-2: BIPSR Process Pillars

Each phase in the BIPSR Process is designed to leverage the information from the previous phases, which builds layers of information about the viability of the candidate standards. As a result, the later subprocesses (V and VI) do not necessarily occur in sequence but are iterated as necessary to produce sufficient information to support the recommendations. Table 4-1 contains a high-level description of various activities that take place in the subprocesses that make up the BIPSR Process.

The timeline associated with implementation of the BIPSR Process is driven by the number of candidate standards identified, the complexity of the candidate standards, and the complexity of the injury type. Additionally, the BIPSR Process can be tailored to support

TABLE 4-1: BIPSR Process Pillar Activities

No.	Subprocess	Activities
I	Review Existing Capabilities	• Engage Stakeholders and identify relevant standards for the injury criteria through a systematic literature survey • Establish a broad-based, independent review panel • Poll the community by issuing a RFI
II	Develop Data Collection Mechanisms	• Develop standardized evaluation and information templates • Conduct frequent panel meetings to establish review criteria
III	Develop Evaluation Criteria	• Define scenarios and evaluation metrics • Hold a consensus-building meeting
IV	Evaluate Candidate Standards	• Conduct an interactive set of evaluations with the SME Panel and developers
V	Host Meeting	• Hold a consensus-building meeting for Stakeholders to share information
VI	Derive and Execute Test Cases	• Involve users and Stakeholders in the development of scenario-based test cases and execute the tests for the identified candidate standards (where applicable)
VII	Develop Recommendations and Evaluate Process	• Produce a report that recommends standards for PCO consideration as the basis for MHS Blast Injury Prevention Standards • Recommend improvements to the BIPSR Process

Photo credit: 1st Lt. Ryan DeBooy/U.S. Army

compressed, quick-turnaround implementation that meets the need and critical nature of specific Blast Injury Types.

The identification and prioritization of the injury mechanisms fall outside the scope of the BIPSR Process and are the responsibility of the PCO and BIPSR Process Stakeholders. The BIPSR Process identifies, but does not resolve, capability gaps in the current standards. These gaps are shared with the DoD medical and non-medical S&T communities.

The PCO developed the BIPSR Process via a series of BIPSR Process Stakeholder meetings and obtained Armed Services Biomedical Research Evaluation and Management (ASBREM) Committee approval.

The Johns Hopkins University Applied Physics Laboratory (JHU/APL), a University-Affiliated Research Center and DoD trusted agent, supported the PCO through the piloting of the BIPSR Process with an evaluation and analysis of Toxic Gas Inhalation as an exemplar. Currently, the MITRE Corporation, a DoD trusted agent that operates a federally funded research and development centers (FFRDC), supports the PCO in the execution of the BIPSR Process by working closely with BIPSR Process Stakeholders and SMEs in the blast community.

BIPSR Process Improvements

Seeking to expedite the timeline required for evaluation of MHS BIPSR Process Blast Injury Type, the PCO developed the BIPSR Process simulation model using the business process modeling notation standard. This standard modeling methodology graphically represents the BIPSR Process activities and facilitates quantitative and qualitative analysis via simulation.

As BIPSR Process milestones are reached with each Blast Injury Type under evaluation, and through feedback from the Stakeholders, modifications and improvements to the BIPSR Process are considered and evaluated for implementation.

In addition, the development and implementation of a web-based collaboration environment known as iBIPSR was initiated to enhance information sharing in real time and to further reduce the timeframe to complete the BIPSR Process for each of the remaining MHS BIPSR Process Blast Injury Types.

iBIPSR Capability

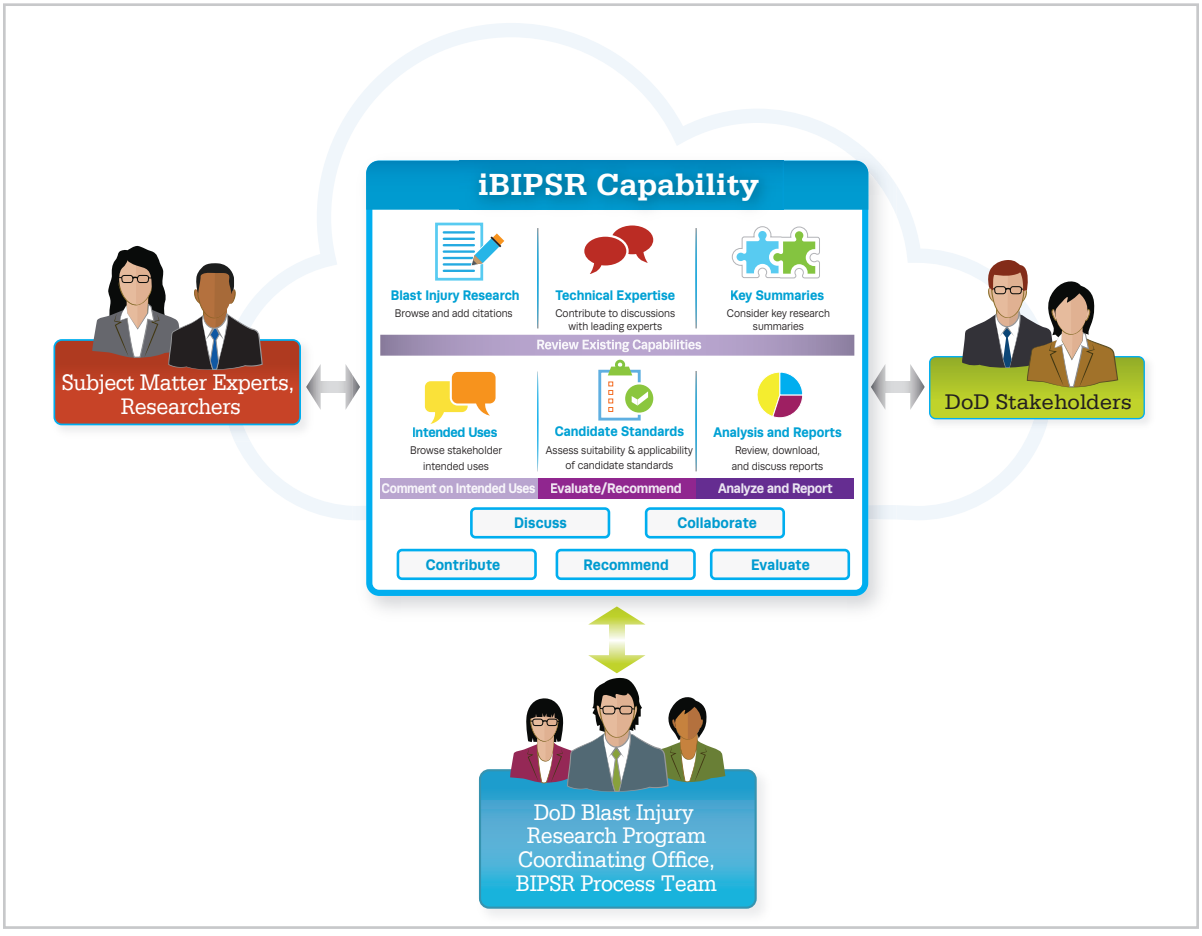
The iBIPSR capability has foundations in collaborative semantic web technology, an information synthesis technology well suited for large, collaborative, multi-user information sharing and decision-making efforts. The iBIPSR site is an online forum developed to enhance information sharing among blast injury experts. The standard wiki format has been enhanced with user-friendly user interfaces, built-in help capability, and an internal feedback mechanism to allow users to report inconsistencies and suggest enhancements.

iBIPSR relies on commercial off the shelf (COTS) software and MITRE developed extensions. The site now follows the COTS upgrade cycle to remain current and improve the security posture.

iBIPSR supports the PCO's EA mission to leverage existing knowledge and foster collaboration among academia, industry, international partners, and government organizations by providing a platform for continuous collaboration throughout the BIPSR Process with the collected wisdom residing on iBIPSR for maximum collaboration.

As shown in Figure 4-3, the iBIPSR capability supports a variety of users engaged in planned collaborative interactions between and among BIPSR Process Stakeholders, SMEs, the PCO, and the MITRE team.

FIGURE 4-3: BIPSR Process Supported by the iBIPSR Site



Additionally, the iBIPSR capability offers transparency by capturing and managing Stakeholder organizations' knowledge gaps and needs, and facilitates understanding through near-real-time communication among participants. The MITRE team has developed the iBIPSR capability using best practices, established standards, and user input. iBIPSR will continue to evolve through user input to meet the knowledge goals of the mission.

Power of iBIPSR

The iBIPSR capability represents a novel way to shorten the timeline of the BIPSR Process without sacrificing decision quality (Table 4-2). Following initial enrollment of the Auditory Focused Stakeholders, the iBIPSR capability has been improved by expanding the user base and dynamically incorporating user feedback to develop and improve site features. Ultimately, the PCO anticipates that all BIPSR Process Stakeholders and designated SMEs will use the iBIPSR capability.

TABLE 4-2: The Power of the iBIPSR Site

The iBIPSR site is well-suited to large, collaborative, multi-user information sharing and decision making:

- Leverages existing knowledge
- Utilizes technology to foster continuous collaboration
- Removes obstacles to participation (*e.g.*, travel and scheduling)
- Allows for broad engagement in the process with access to information used in all stages of the BIPSR Process

MHS BIPSR Process Blast Injury Type Prioritization

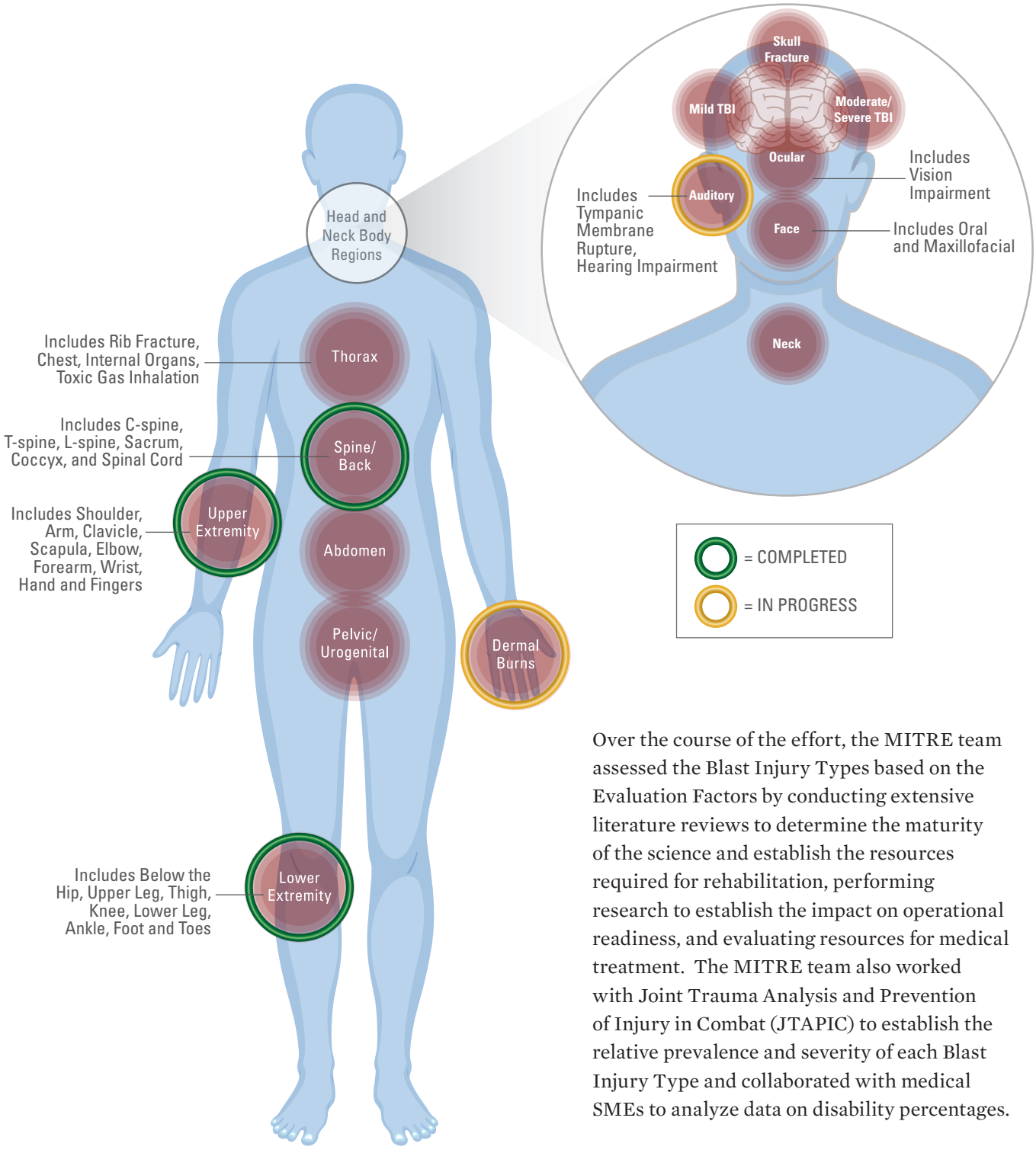
Through a series of initial BIPSR Process Stakeholder Meetings hosted by the PCO, BIPSR Process Stakeholders categorized a total of 14 MHS BIPSR Process Blast Injury Types based on specific body regions (Figure 4-4). This represented a shift from an older classification of injury types that referred to individual organs and bones (as described in a 1989 Walter Reed Army Institute of Research (WRAIR) report).

To confirm that the needs of the DoD were being met, the BIPSR Process team applied a mathematical methodology, using Stakeholder inputs, to establish a priority ranking of the Blast Injury Types that determined the initial order for executing the BIPSR Process. This Blast Injury Type prioritization methodology assessed and rated each MHS BIPSR Process Blast Injury Type against six Evaluation Factors that were developed by the BIPSR Process Stakeholders and are defined in Table 4-3. As of FY18, the Lower Extremity, Spine and Back, and Upper Extremity Blast Injury Types are complete and the BIPSR Process has been initiated for the Auditory and Dermal Burns Blast Injury Types.

To ensure the current needs of the operational environment and the DoD are being met, the PCO has performed a reprioritization effort for the remaining nine MHS BIPSR Process Blast Injury Types: Ocular, Face, Neck, Thorax, Abdomen, Pelvic/Urogenital, Skull Fracture, mTBI, and Moderate to Severe TBI. The reprioritization effort applied an established mathematical analysis technique, multi-attribute utility theory (MAUT), a widely used, widely accepted methodology for guiding tradeoffs among multiple objectives.

This reprioritization effort again assessed the remaining MHS BIPSR Process Blast Injury Types against the six BIPSR Process Evaluation Factors that had been developed and used in the initial prioritization effort (Table 4-3). The Evaluation Factors and scoring scales used in the MAUT methodology provide a framework for capturing subjective assessments to support an objective and unbiased decision-making process.

FIGURE 4-4: Categorization of MHS BIPSR Process Blast Injury Types by Body Region



Over the course of the effort, the MITRE team assessed the Blast Injury Types based on the Evaluation Factors by conducting extensive literature reviews to determine the maturity of the science and establish the resources required for rehabilitation, performing research to establish the impact on operational readiness, and evaluating resources for medical treatment. The MITRE team also worked with Joint Trauma Analysis and Prevention of Injury in Combat (JTAPIC) to establish the relative prevalence and severity of each Blast Injury Type and collaborated with medical SMEs to analyze data on disability percentages.

BIPSR Process Stakeholders provided inputs to the reprioritization process so the results reflect current DoD priorities.

TABLE 4-3: BISPR Process Evaluation Factors

Evaluation Factor	Description
Impact on Operational Readiness	The time for a Service member to return-to-duty (RTD).
Blast Injury Prevalence Rate	The number of cases of a given Blast Injury Type expressed as a percentage of the total number of blast injuries.
Treatment Resources	Roles of medical treatment, which are the distribution of medical resources and capabilities to provide Service member's medical care.
Maturity of the Science	Determined by the existence of established standards (*e.g.*, Military Standard (MIL-STD)-1474E Noise limits design criteria) or, in the absence of established standards, by the degree to which biomedically-valid injury mechanisms have been published in the peer-reviewed scientific literature, or by the development and application of assessment methodologies based on the established injury mechanisms to assess injury risks.
Rehabilitation Resources	Resources required to support a Service member's rehabilitation beyond immediate treatment resources and may include therapy, pharmaceuticals, or devices needed to reset for quality of life (QOL).
Disability Percentage	Designated percentage assigned to an injury type when calculating disability benefits.

In the final step of the exercise, a score was calculated, using the MAUT methodology, for each Blast Injury Type, resulting in a new rank order.

Next Steps for Prioritization Effort

The PCO plans to share the results of the reprioritization exercise at the next BIPSR Process Stakeholder Committee Meeting, and to continue execution of the BIPSR Process based on their recommendations.

Update on Implementation of the BIPSR Process for MHS BIPSR Process Blast Injury Types

BIPSR Process for the Auditory Blast Injury Type

The BIPSR Process for the Auditory Blast Injury Type is in progress, and, as previously noted, is being used as an exemplar to prove out the iBIPSR capability. As a part of the initial steps of the BIPSR Process, the MITRE team completed the Existing Capabilities Review of the Auditory Blast Injury Type: performing an in-depth literature survey, posting a request for information (RFI) on the Federal Business Opportunities (FedBizOpps) website, and interviewing SMEs from industry, academia, and government agencies. The PCO also established the Auditory Focused Stakeholder Committee, thus far comprising 14 members representing the Army, Navy, Air Force, Marine Corps, Department of Veterans Affairs (VA), and the materiel development, operational, T&E, and medical communities of interest. The Auditory Focused Stakeholder Committee members drive all major decisions for the BIPSR Process Auditory Blast Injury Type.

During the second Auditory Focused Stakeholder Committee Meeting in FY16, participants concurred with the MITRE team's recommendation to continue the BIPSR Process for the Auditory Blast Injury Type by convening a SME Panel of auditory experts to independently evaluate the existing capabilities.

Photo credit (opposite page): Capt. Joseph Legros/U.S. Army

The PCO subsequently supported the assembly of the BIPSR Process Auditory SME Panel whose members are drawn from industry, academia, and government. Aligned with the BIPSR Process, these SMEs have experience in the domain of interest, development of the candidate standard product (*e.g.*, dose-response curve, computational model), T&E, clinical medicine, and IV&V.

The first meeting of the BIPSR Process Auditory SME Panel took place on September 19–20, 2017. During Meeting 1, the MITRE team introduced the SME Panel to the BIPSR Process, iBIPSR, and the findings to-date. After this introduction, the MITRE team worked with the SME Panel to revise the Intended Uses of a Candidate Standard (which were provided by the Stakeholders) and Evaluation Criteria in preparation for the independent Candidate Standards evaluation.

The second meeting of the BIPSR Process Auditory SME Panel was held on February 27, 2018. During Meeting 2, the MITRE team reviewed the Candidate Standard Evaluation Methodology, and the SME Panel discussed and updated the Evaluation Factors. At the end of the meeting, the MITRE team provided information about the next steps in the BIPSR Process, including finalizing the Evaluation Factors.

During SME Panel Meeting 3 on July 31 and August 1, 2018, the Panel reviewed its activities to date; the Evaluation Methodology and Findings, Evaluation Criteria, and Candidate Standards; and finalized the evaluation materials. The SME Panel discussed topics influencing the relative importance of different Evaluation Factors and discussed information that would be needed on the Candidate Standards in order to complete the evaluation. The SME Panel established the weights and scoring levels that will be used to evaluate the Candidate Standards.

Next Steps for Auditory Blast Injury Type
The PCO plans for the next SME Panel Meeting in Q1 FY19. The planned agenda includes discussion of the Candidate Standards information collected from the Candidate Standard Developers/ Champions. Following this meeting, the next steps of the BIPSR Process include the SME Panel evaluating the Candidate Standards using the Evaluation Factors and the Candidate Standard Information template, then applying MAUT to analyze the information. Following these steps, the SME Panel will develop and execute on a draft recommendation, including a T&E plan for further independent evaluation of the Candidate Standards. In the final steps of the BIPSR Process, the PCO will host a Consensus Building meeting with Stakeholders, Candidate Standard Developers and Owners, and government SMEs to allow for discussion and further investigation of the recommended actions.

BIPSR Process for Dermal Burns Blast Injury Type

The BIPSR Process for the Dermal Burns Blast Injury Type has been initiated per the recommendation of the BIPSR Process Stakeholders, and following the initial steps of the BIPSR Process, the Existing Capabilities Review is in progress. Early activities included literature review and identifying potential SMEs for interviews.

Next Steps for Dermal Burns Blast Injury Type
Following the SME interviews, which will ensure a thorough understanding of the current state of the science, DoD Stakeholders will be invited to convene the Dermal Burns Focused Stakeholder Committee, which will drive the activities and decisions of the BIPSR Process. Once convened, the Focused Stakeholders will issue an RFI relating to potential injury prediction/simulation standards to ascertain a broad canvassing of the community. Interviews with Focused Stakeholders following Committee Meeting #1 will provide their Intended Uses for an MHS Blast Injury Prevention Standard for Dermal Burns. An analysis of the Intended Uses against identified Candidate Standards will inform next steps in the BIPSR Process.

Way Forward

In the coming year, the PCO plans to organize and host a Consensus Building Meeting for the Auditory Blast Injury Type. This meeting is the culmination of the Auditory Blast Injury Type evaluation of MHS Auditory Blast Injury Prevention Candidate Standards identified through the BIPSR Process. Following the steps of the BIPSR Process, after the SME Panel members independently evaluate the Candidate Standards, the PCO expects to further evaluate Candidate Standards through an independent T&E process, resulting in recommendations by the SME Panel. The subsequent Consensus Building Meeting with BIPSR Process Stakeholders, Candidate Standard developers and champions, government, academia, and industry SMEs will provide an opportunity to discuss the recommendation and next steps.

To enhance BIPSR Process capabilities, the PCO plans to incorporate lessons learned from proving-out the iBIPSR capability using the Auditory Blast Injury Type as an exemplar. The PCO provided iBIPSR access to the Auditory Focused Stakeholders, as well as the SME Panelists, and plans to expand access to Stakeholders in FY19. The PCO anticipates moving forward with the iBIPSR capability on future BIPSR Process Blast Injury Type evaluations.

The PCO plans to establish the Dermal Burns Focused Stakeholder Committee to drive the Dermal Burns BIPSR Process activities. Focused Stakeholders will identify Intended Uses and Requested Functionalities for an MHS Dermal Burns Blast Injury Prevention Standard.

Following the steps of the BIPSR Process, literature review and interviews with SMEs from government, academia, and industry will guarantee a thorough understanding of the current state of the science.

Following the Reprioritization effort which analyzed current literature, Stakeholder input, and data from JTAPIC and other government sources, the PCO plans to execute the remaining MHS BIPSR Process Blast Injury Types in the new rank order

Photo credit: Janine Fabre/DVIDSHUB

which reflects the current needs of the DoD. The information gained from investigating each MHS BIPSR Process Blast Injury Type through the reprioritization effort has led to a baseline understanding of the current maturity of the science for each Blast Injury Type, which will improve efficiency of evaluation through the BIPSR Process.

Ultimately, the knowledge gaps revealed, and the recommendations developed through the BIPSR Process will enable the DoD to apply MHS Blast Injury Prevention Standards that support weapon system health hazard assessments, combat platform occupant survivability assessments, and protection system development and performance testing. The S&T knowledge gaps identified for these MHS BIPSR Process Blast Injury Types will be shared with the medical research community to inform the development of future MHS Blast Injury Prevention Standards.

05

CHAPTER 5:

INFECTIOUS DISEASE CLINICAL RESEARCH PROGRAM: BLAST-RELATED INFECTIONS RESEARCH

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For many warfighters injured in blast, wound infection is a consequential and dangerous condition not manifested in the immediate aftermath of the blast that may jeopardize the life and well-being of the warfighter and imperil his or her ability to return to duty. The particular circumstances of blast injury – penetration of host defenses, possibly accompanied by extensive burns and compromised immunity, implanting of foreign bodies through secondary blast injury, and hypoxic tissue damage or necrosis – enhance the danger of infection.

This problem is longstanding. Throughout every war in history, wound infections have commonly followed battlefield trauma (*Murray, Hinkle et al., 2008*). Although wounded warriors and civilian trauma patients have similar challenges, the nature of battlefield trauma adds further complexity due to the severity of the injuries, as well as the high frequency of polytrauma. Wounded warriors who experience blast trauma are even more likely to develop wound infections (*Ficke, Eastridge et al., 2012, Krueger, Wenke et al., 2012, Belmont, Owens et al. 2016, Weintrob, Murray et al., 2018*).

The urgency of understanding and treating blast-related wound infections has grown in recent years. Significant achievements in combat casualty care have resulted in a lower overall case fatality rate (*i.e.*, a lower percentage of fatalities among all those wounded in action, including those who died before being hospitalized) for injuries sustained in Iraq (Operation Iraqi Freedom; OIF) and Afghanistan (Operation Enduring Freedom; OEF). Increased infection burden accompanied the higher hospitalization rate (*Petersen, Riddle et al., 2007, Murray, Wilkins et al., 2011, Tribble, Conger et al., 2011, Yun, Murray et al., 2016, Weintrob, Murray et al., 2018*): about one-third of combat casualties injured in OIF and OEF developed at least one trauma-related infection, as did more than half of those severely injured enough to be admitted to a U.S. military hospital intensive care unit (*Weintrob, Murray et al., 2018*). Again, the situation is particularly acute for cases of blast injury: in one study, 41% of patients injured by an improvised explosive device (IED) developed one or more infections, versus 24% of patients injured by non-blast means (such as gunshots) (Figure 5-1; *Weintrob, Murray et al., 2018*).

Moreover, the increased survival rate results in patients presenting with particularly challenging and dangerous disease processes, such as invasive fungal wound infections (IFIs) and multidrug-resistant organisms (MDROs) (*Murray, Yun et al., 2009, Hospenthal, Crouch et al., 2011, O'Shea 2012, Paolino, Henry et al., 2012, Tribble and Rodriguez 2014*).

In particular, infections complicating open fractures inflict terrible losses on military personnel resulting, in some cases, in prolonged use of antibiotics, extended hospitalization, multiple surgeries, and late amputations (*Huh, Stinner et al., 2011*). There is a concomitant cost to military readiness and lethality because these personnel are slower to return to duty (*Napierala, Rivera et al., 2014*). Furthermore, there is a risk of new or recurrent infections developing long after the patient has been discharged from the hospital (*Yun, Branstetter et al., 2008, McDonald, Liang et al., 2018, Tribble, Krauss et al., 2018*). These costs may be more exorbitant on future battlefields in which U.S. air superiority is not assured and mission conditions are restrictive, thus reducing opportunities for medical evacuation, prolonging field medical care, and necessitating a rapid return to duty in the field (*Keenan and Riesberg 2017*).

Consequently, improving the care of blast casualties and further understanding the short- and long-term impact of blast-related wound infections is a top priority of the Military Health System (MHS). Increased awareness

Photo credit (opposite page): Airman 1st Class Laura Max/ U.S. Air Force

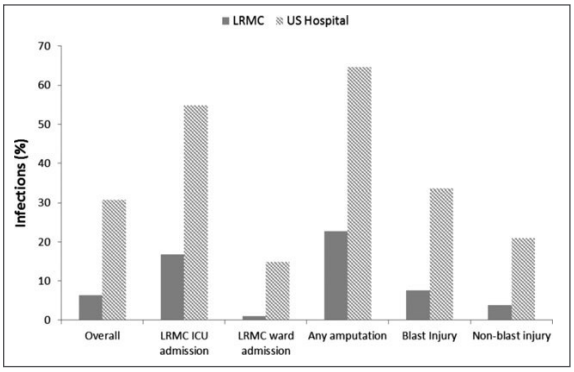

FIGURE 5-1: Infection is a significant burden on the injured warrior in today's conflicts; these data reflect the TIDOS population from 2009-2012. Graph from (*Weintrob, Weisbrod et al., 2015*)

and clinical support tools are necessary in the forward-deployed setting to assist providers with infection prevention and management, particularly in scenarios demanding prolonged field care. A collaborative clinical research network is key for filling knowledge gaps related to the prevention and management of blast-related wound infections.

Infectious Disease Clinical Research Program and Trauma-Related Infections Research

In 2005, the Infectious Disease Clinical Research Program (IDCRP) was established through an Interagency Agreement between the Uniformed Services University of the Health Sciences (USU) and the National Institute of Allergy and Infectious Diseases (NIAID) as a clinical research center to address infectious disease threats of military relevance, as well as to bridge clinical research efforts between the Department of Defense (DoD) health surveillance and warfighter product development efforts. The IDCRP investigators collaborate with partners from the DoD, U.S. government interagency, academia, and industry to conduct research focused on filling knowledge gaps related to the control and prevention of infectious disease in military Service members and DoD beneficiaries.

Because of the high proportion of infectious complications among combat casualties from Iraq and Afghanistan, it was recognized that there was a need to collect comprehensive trauma-related infection data to understand the impact and to improve management for these infections on wounded warriors and the MHS. As a result, IDCRP developed the Trauma-Related Infections Research Area to focus on this critical need. The four main aims of the research area are: (1) to describe the epidemiology, clinical characteristics, and outcomes among combat blast-related wounds and infections; (2) to compare clinical outcomes and antibiotic exposure to specific microbiological factors in colonizing or infecting organisms isolated from trauma patients; (3) to evaluate short- and long-term health impacts of combat-related infections through ongoing care in DoD and/or Veterans Affairs (VA) following initial discharge; and (4) to assess adherence and outcomes to Joint Trauma System (JTS) Clinical Practice Guidelines and antibiotic stewardship in support of the U.S. strategy in Combating Antibiotic-Resistant Bacteria.

Trauma Infectious Disease Outcomes Study (TIDOS)

The foundation of the Trauma-Related Infections Research Area, is the DoD – VA Multicenter Cohort Study Evaluating Infection-Associated Clinical Outcomes in Hospitalized Medical Evacuees following Traumatic Injury (commonly known as the Trauma Infectious Disease Outcomes Study or TIDOS) (*Tribble, Conger et al., 2011*). The overall goal of TIDOS is to evaluate the short- and long-term consequences of trauma-related infections among military personnel with deployment-related injuries, in relation to prevention and treatment.

Photo credit: Senior Airman Tiffany Trojca/U.S. Air Force

TIDOS collects useful and militarily-relevant data by focusing on Wounded Warriors who:

- Are active-duty Service members or DoD beneficiaries over 18 years of age
- Suffered an injury while deployed between June 1, 2009 and December 31, 2014
- Required medical evacuation to Landstuhl Regional Medical Center (LRMC) in Germany
- Transitioned to medical care at Brooke Army Medical Center (BAMC) in San Antonio, TX, or at the Walter Reed National Military Medical Center (WRNMMC, formerly Walter Reed Army Medical Center and National Naval Medical Center prior to September 2011) in Bethesda, MD

Infection-related data (*e.g.*, infection diagnoses, antimicrobial treatment, and microbiology) were collected from all patients admitted to participating hospitals through the TIDOS infectious disease module created to supplement the DoD Trauma Registry, which is an innovation of the Joint Trauma System to collect data from wounded military personnel across different levels of care. Patients were also given the opportunity to enroll in a cohort during their initial hospitalization, which followed the patient after hospital discharge, enabling assessment of the long-term outcomes and evaluation of ongoing infection risk. Those patients who left active duty service were given the option to consent to continue to participate through VA electronic medical record longitudinal review, reducing the loss of patients from the study and maintaining visibility of the warfighter's well-being even after transition from the military. From June 1, 2009 to December 31, 2014, 6,079 wounded warriors were admitted to LRMC, and 2,699 of those transferred to BAMC or WRNMMC. Most of the patients were young men (median age 25 years) and most were injured while supporting operations in Afghanistan. More than half were classified with severe-to-critical injuries, about one-fifth suffered traumatic amputation, and about three-quarters had at least one open fracture (not considering fingers and toes).

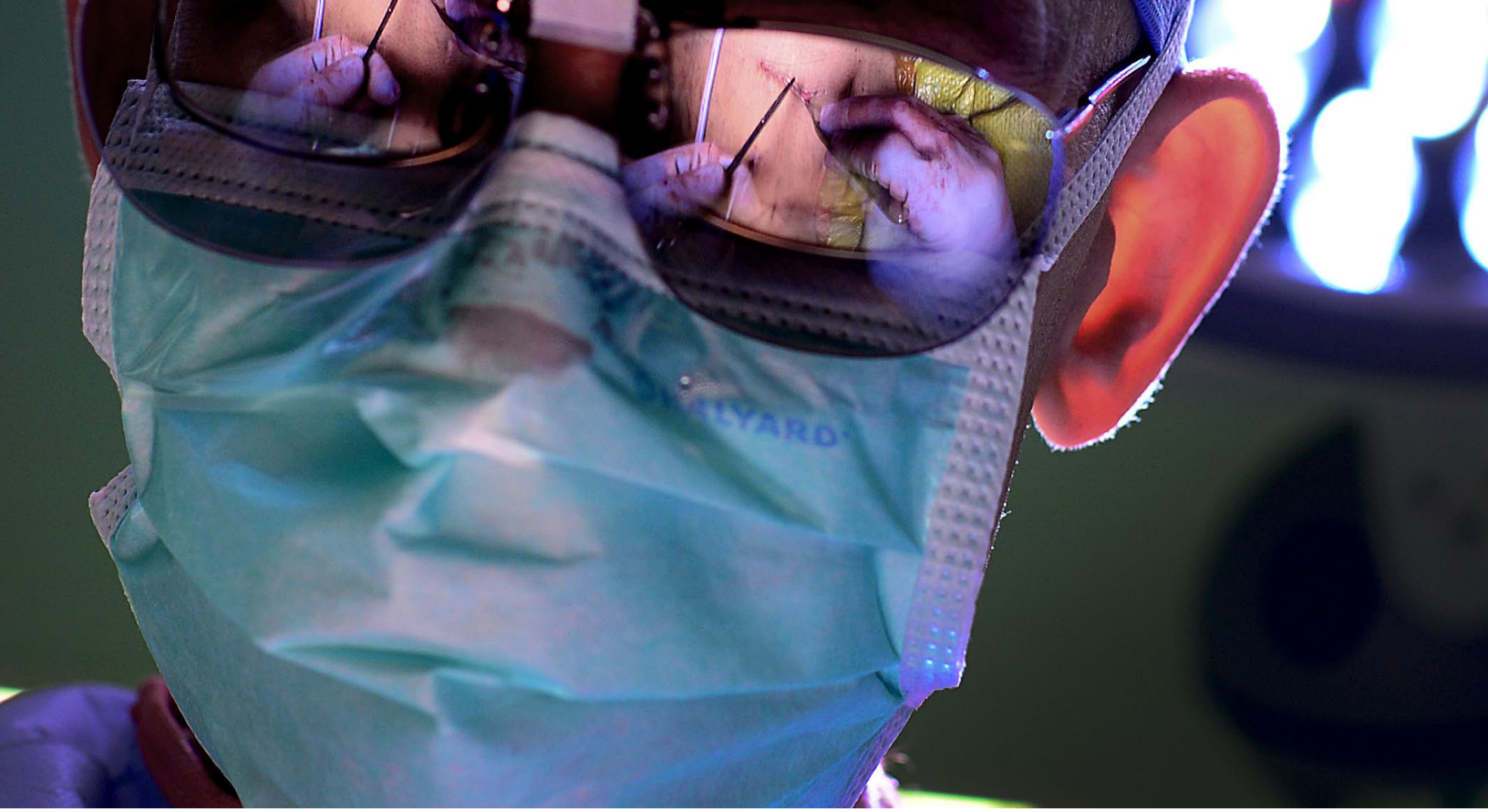

Photo credit: Tech. Matthew Plew/U.S. Air Force

Collaborations and Partnerships

The size and scope of TIDOS gives researchers a wide-ranging view of wound infection from combat injuries, including blast. That view can be enhanced by considering warfighters from Allied Nations with similar exposures and patient histories. To that end, the IDCRP Trauma-Related Infections Research has engaged with multiple collaborations and partnerships associated with blast trauma-related research within the DoD, encompassing a wide range of medical/surgical specialties across military hospitals and research commands. A long-standing collaboration with the Veterans Administration (VA) St. Louis Health Care System has contributed significantly to the understanding of the long-term impact of trauma-related infections on wounded warriors. A collaboration with the United Kingdom Ministry of Defence Wound Infections Surveillance Programme is underway to conduct comparative analyses in order to determine best practices for the management of trauma-related infections.

Blast-related Wound Infections

The large patient pool from TIDOS gives military researchers a tool with which to properly focus research attention and efforts; the size and scope of the study powers useful generalizations about the challenges facing the wounded.

TIDOS is a powerful tool for examining infections subsequent to blast injury. Almost half of the patients admitted to LRMC were injured via blast. Among the patients who transferred from LRMC to BAMC or WRNMMC, almost two-thirds had blast injuries. The data indicate the importance of understanding infection as a part of blast injury treatment: about a quarter of patients with blast trauma were diagnosed with at least one trauma-related infection, with an average of 2.5 infections among them. Skin and soft-tissue infections (SSTIs) and bone infections (osteomyelitis) were the most common type of infection: ~30% of blast patients admitted to participating U.S. hospitals. In most cases, infections manifest between three and 11 days after injury and are a crucial part of blast injury care. Analysis of the TIDOS blast trauma population highlights particular patterns of injury and infection, and those patterns inform the relevance of trauma-related infections study to the treatment of blast injury. Notably, blast injury patients present specific challenges for

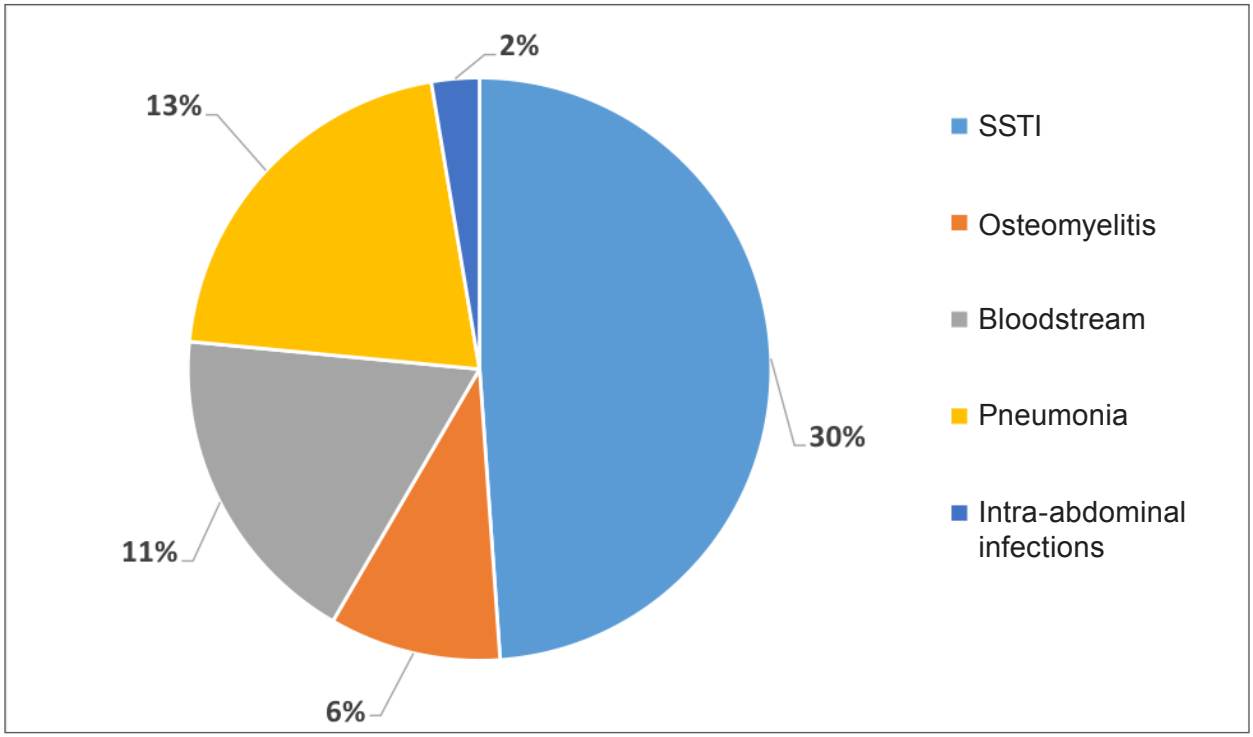

FIGURE 5-2: Frequency of trauma-related infections among wounded warriors with blast injuries admitted to U.S. hospitals. STTI – skin and soft-tissue infection. Percentages are all of blast injury patients admitted to U.S. hospitals participating in TIDOS. Patients may have more than one type of infection.

extremity wound infections, IFIs, and multidrug resistance, each of which are expounded upon below.

Extremity Wound Infection

Extremity wounds – wounds of the arms and legs – are the most common battlefield injuries and carry a high risk of infection, particularly with open fractures and amputations (*Brown, Murray et al., 2010, Murray, Obremskey et al., 2011, Tribble, Lewandowski et al., 2018, Weintrob, Murray et al., 2018*). These types of injuries are frequently a consequence of explosive blast detonation. For example, a new injury pattern emerged during OEF, Service members were proportionally more likely to be injured by an improvised explosive device (IED) while on foot patrol ("dismounted"). These dismounted complex blast injuries are characterized by a traumatic amputation of one lower extremity, substantial injury to the other lower extremity, injuries to the pelvic and/or genital region, and injuries to an upper extremity (*Ficke, Eastridge et al., 2012*). As such, it is unsurprising that extremity wound infections –SSTIs and osteomyelitis (the infection of bone tissue) – plague about one-third of blast injury patients admitted to U.S. hospitals, and make up the majority of all infections among these patients (Figure 5-2). These statistics motivate recently completed TIDOS analyses that focus on extremity wound infections over a three-year period with regard to epidemiology, wound microbiology, infection risk factors, and antibiotic practice patterns (*Stewart, Shaikh et al., 2015, Stewart, Shaikh et al., 2016, Stewart, Shaikh et al., 2016, Stewart, Blyth et al., 2018, Stewart, Shaikh et al., 2018*). Improved injury profile and wound severity classification is providing more refined means to assess infection risks and outcomes relative to surgical and medical care.

Osteomyelitis is a serious complication of open fractures that frequently requires prolonged use of antibiotics, multiple surgical procedures, and extended hospitalization. Because of this severity, the Trauma-Related Infections Research Area has conducted a separate study of osteomyelitis. As part of this protocol, characteristics and risk factors for osteomyelitis,

and recurrence after resolution of the initial infection, were examined in combat casualties with open fractures (70% injured via a blast mechanism) over a six-year period (2003-2009), focusing on open fractures of the tibia, femur, and arm long bones (*Lewandowski, Potter et al., 2018, Petfield, Tribble et al., 2018, Tribble, Lewandowski et al., 2018*). Open fractures of the tibia carry the highest risk of infection and patients who sustained a below knee amputation had a 15 times greater risk of developing osteomyelitis. In addition, patients with open tibia fractures who had significant muscle damage with either loss of muscle function or dead muscle were 8 times more likely to develop osteomyelitis. The analysis also demonstrated that patients with an open tibia fracture who were injured via a blast were two-to-three times more likely to develop osteomyelitis (*Tribble, Lewandowski et al., 2018*). The findings correspond with studies of civilian trauma, which have identified increased fracture severity as a predictor of osteomyelitis (*Bowen and Widmaier 2005, Kortram, Bezstarosti et al., 2017, Thakore, Francois et al., 2017*). Planned analyses will merge the Trauma-Associated Osteomyelitis and TIDOS databases to provide comprehensive assessment (>10 years) of characteristics and risk factors for osteomyelitis following battlefield injury.

Assessment of deep soft-tissue infections is another area of ongoing TIDOS research. An analysis was initiated during 2018 to assess outcomes among patients with deep soft-tissue infections based on different treatment regimens involving commonly used antibiotics (*i.e.*, carbapenem and vancomycin). Approximately 95% of the study population was injured via blast. The findings will be used, along with other published reports, to support best practices for the management of infections.

Invasive Fungal Wound Infections

Following the surge of troops into Afghanistan in 2009/2010, there was an unexpected outbreak of IFIs among combat casualties with blast trauma, particularly among those with dismounted complex blast injuries. Fungal wounds are particularly troublesome and injurious to warfighters; they present treatment challenges and the antifungals used in treatment may have significant side effects (*Barrett, Vardulaki et al., 2003, Tan, Brayshaw et al., 2006, Hamill 2013, Tribble and Rodriguez 2014, Xing, Chen et al., 2017*). Because IFI manifests more commonly in more severe injuries, it has been difficult to quantitate the additional challenge of fungal infection.

Consequently, a DoD investigation into the outbreak was led by TIDOS investigators, who assessed patients with IFIs diagnosed between June 2009 and December 2010 (*Warkentien, Rodriguez et al., 2012*). Common characteristics among the patients were identified, including being injured via blast (primarily dismounted), having a traumatic lower extremity amputation, and requiring large-volume blood transfusions within 24 hours of injury (average of 30 units of blood). An important finding from the outbreak investigation was the identification of a suspicious wound based on recurrent tissue necrosis following surgical debridements, which is the hallmark of an IFI. Findings were presented to the Assistant Secretary of Defense (Health Affairs), Surgeons General, and Combatant Command (COCOM) Surgeons in 2011 and led to the standardized capture of fungal infection-related data, including notations on occurrence of wound necrosis, histopathology results, and use of antifungal therapy. The information was used by the JTS in the development of a clinical practice guideline for the prevention and management of IFI wounds in combat casualties in 2012 (*Joint Theater Trauma System, 2012*). These recommendations are vital because early and aggressive treatment can be essential for managing IFIs (*Tribble and Rodriguez, 2014*).

Extending the study period to approximately two years, 77 patients with IFIs were identified

(6.8% of 1,133 combat casualties admitted to LRMC between June 2009 and August 2011). Epidemiology, risk factors, clinical outcomes, diagnostics, and mycology related to IFIs were assessed using this population (*Lloyd, Weintrob et al., 2014, Rodriguez, Weintrob et al., 2014, Rodriguez, Weintrob et al., 2014, Tribble and Rodriguez 2014, Tribble, Rodriguez et al., 2015, Warkentien, Shaikh et al., 2015, Weintrob, Weisbrod et al., 2015, Heaton, Weintrob et al., 2016, Lewandowski, Weintrob et al., 2016*). Patients who had a blast injury were 5.7 times more likely to develop an IFI with the risk increasing to 8.5 times more likely when the patients were injured by a blast while on foot patrol; reflecting the pattern of injury characteristic of Soldiers and Marines injured during OEF. Sustaining a traumatic above-knee amputation and requiring a massive amount of blood volume (≥20 units) within 24 hours of injury also carries a high risk of developing an IFI (*Rodriguez, Weintrob et al., 2014*). These findings can be used to identify patients at high risk, leading to earlier diagnosis and treatment.

Another key finding of the analyses was that wounds with an IFI took approximately a week longer to heal, and required significantly more surgical amputations or amputation revisions, compared to wounds with no infection (*Lewandowski, Weintrob et al., 2016*). When compared to wounds with a bacterial infection, it took approximately four days longer for IFI wounds to heal. The findings also demonstrate that certain molds (*i.e.*, mold from the order Mucorales) had greater negative impact on wound healing and underscore the importance of developing and refining good practices for the management of IFIs (*Warkentien, Shaikh et al., 2015*). Therefore, the JTS asked TIDOS investigators to assist with revising and refining the existing IFI clinical practice guidelines based on the findings of the TIDOS IFI analyses (*Rodriguez, Tribble et al., 2016, Rodriguez, Tribble et al., 2018*).

A comprehensive review of characteristics of patients that had laboratory evidence of a fungal infection (wound culture and/or histopathology) indicated that a portion of the patients with early evidence of fungi may have been colonized rather than developing an infection. This observation led to the refinement of the IFI definition and classification to include the timing of fungal laboratory evidence (*Ganesan, Shaikh et al., 2017*). Specifically, the IFI definition was revised to more explicitly specify laboratory evidence of a fungal infection, requiring that it follow at least two surgical debridements when wound necrosis is evident and ongoing (Figure 5-3). This refinement provides greater clinical utility to the IFI classification scheme, further emphasizing which patients need targeted surgical and medical management (*Ganesan, Shaikh et al., 2017*). In 2018, assessment of IFI epidemiology using the new classification was completed and next steps involve further assessment of risk factors and outcomes. Moreover, a comparative analysis of IFI cases between American and British military personnel is planned, to support best practices for prevention.

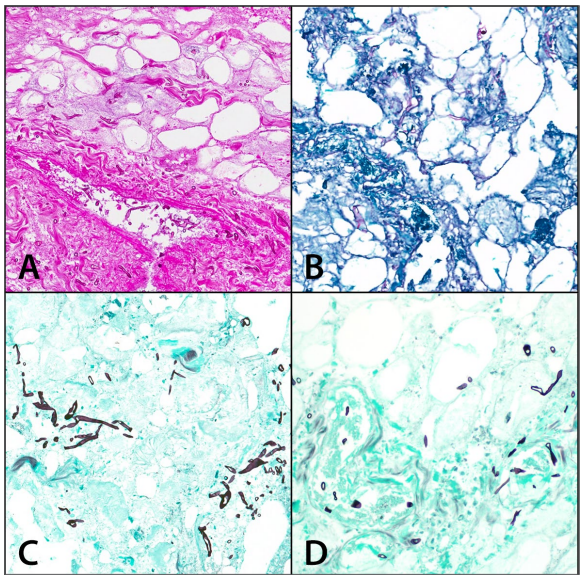

FIGURE 5-3: Necrotic tissue with mucormycetes identified by different staining methods. Originally published by BMC (*Heaton et al., 2016*).

Early identification of IFIs is paramount to a successful outcome. Thus, the objective of another protocol under the Trauma-Related Infections Research Area has been to assess molecular diagnostics methods, which are considerably more rapid than traditional culture methods, for the detection of fungus in archived surgical pathology specimens. The analysis of two polymerase chain reaction (PCR)-based assays using tissue specimens with positive histopathology was recently completed, and the findings presented to a panel of subject-matter experts on November 1, 2017. Overall, the assay was determined to be highly specific for detecting mold (99%), but not as sensitive (63%). Sensitivity did improve to 83% in specimens that were collected from sites with documented angioinvasion (*Ganesan, Shaikh et al., 2018, Ganesan, Shaikh et al., 2018*). The *Tissue-Based Molecular Diagnostics Evaluation in Combat-Related Invasive Fungal Wound Infections* Technical Report was also presented to the JTS for review and incorporation into recommendations. Additional analyses are planned to further assess the PCR-based assays by including specimens from IFI patients who were diagnosed based on culture results rather than histopathology, as well as considering serial specimens over time to determine when use of the assay would provide the most accurate result.

Multidrug Resistance and Complex Wound Microbiology

During the wars in Iraq and Afghanistan, there has been an increase in infections involving MDROs, which further complicated care and frequently led to longer hospitalizations, delayed wound healing, and greater resource utilization. An additional challenge was the occurrence of wounds and infections that were polymicrobial. As a result, improved understanding of the complex microbiology of war wounds became a priority of the Trauma-Related Infections Research Area. The TIDOS project established a microbiological repository to retain bacterial and fungal isolates recovered through infection control surveillance and diagnostic evaluations. The TIDOS Microbiological Repository contains more than 8,000 isolates collected from surveillance swabs to detect colonization and from infection clinical work-ups. Approximately 30% of the isolates were classified as multidrug-resistant; that is, to generate analytical solutions, the Trauma-Related Infections Research Area has amassed both a large set of patient histories and data, and a vast corresponding set of infectious organisms for microbiological study.

The large collection of specimens collected through TIDOS are being used as part of the TIDOS Multidrug-Resistant and Virulent Organisms (MDR/VO) Trauma Infections Initiative. This study is a collaborative effort between USU, BAMC, the U.S. Army Institute of Surgical Research, the Walter Reed Army Institute of Research, and the Naval Medical Research Center. The objective of the MDR/VO Trauma Infections Initiative is to enhance the understanding of complex polytrauma and polymicrobial wounds, using specimens contained in the TIDOS Microbiological Repository linked to clinical data. Ultimately, these analyses can be used to sharpen research focus and to generate improved treatment guidelines: characteristic organisms or patterns of organisms associated with infections and characteristic patterns of drug resistance can be identified and addressed.

Areas of research under the MDR/VO Trauma Infections Initiative include the combat wound bacterial microbiome, clinical impact of biofilm production, difficult-to-treat pathogens, emergence of antimicrobial resistance, wound bacteria interaction and antagonism, and MDR/VO wound infection clinical outcomes. Particular emphasis is placed on ESKAPEE pathogens (*Enterococcus faecium, Staphylococcus aureus, Klebsiella*

Photo credit: Airman 1st Class Jason Ridder/U.S. Air Force

pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, Enterobacter species, and Escherichia coli), which are considered public health threats due to increasing resistance in recent years and are emphasized by the Centers for Disease Control and Prevention (CDC) (*Boucher, Talbot et al., 2009, Centers for Disease Control and Prevention 2013*). In the three-year TIDOS population, ESKAPEE pathogens were frequently isolated from infection work-ups. *E. faecium* contributed 10%, 8%, and 6% to the total organisms recovered for SSTIs, osteomyelitis, and bloodstream infections. *Acinetobacter calcoaceticus baumannii* was also common (9%, 11%, and 9% for organisms isolated from SSTIs, osteomyelitis, and bloodstream infections, respectively), as was *E. coli* (10%, 9%, and 7%, respectively) and *P. aeruginosa* (10%, 10%, and 7%, respectively) (*Weintrob, Murray et al., 2018*).

Examination of microbiology of extremity wound infections from the three-year TIDOS population has been completed. The analysis assesses and compares the microbiology of patients with confirmed extremity wound infections, suspected extremity wound infections, and no extremity wound infections. Approximately 64% of the confirmed infections were polymicrobial, with *Enterococcus spp., E. coli, Enterobacter spp., and Pseudomonas spp.* the most frequently detected. Among monomicrobial infections, *Acinetobacter spp., Pseudomonas spp., Enterococcus spp., and Enterobacter spp.* were the most commonly recovered (*Stewart, Shaikh et al., 2016*). The high proportion of polymicrobial wound infections is consistent with other analyses that find blast wounds to frequently have both Gram-negative and Gram-positive organisms, particularly ESKAPEE pathogens, as well as molds (*Wallum, Yun et al., 2015, Warkentien, Shaikh et al., 2015*).


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Serial specimens also confirmed that the wound microbiology changed over time (*Stewart, Shaikh et al., 2016*). These findings corroborate prior studies that demonstrate the complex nature of combat wounds and how organisms recovered at the time of injury are frequently not the same as the organisms associated with infections (*Murray, Roop et al., 2006, Sheppard, Keiser et al., 2010, Wallum, Yun et al., 2015, Valentine and Viacheslav 2017*).

Because *Enterococcus spp.* are among the most common organisms identified from polymicrobial infections, the organisms have been a focus of multiple MDR/VO Trauma Infections Initiative analyses assessing the wound bacterial microbiome. Assessment of patients with *Enterococcus spp.* extremity wound infections found them to be more severely injured (*e.g.*, more units of blood transfused within 24 hours of injury, admissions to the intensive care unit, and operating room visits) and to have a longer period of hospitalization (median of 55 days vs. 40 days), when compared to a population of patients who had infections with organisms other than *Enterococcus spp.* (*Heitkamp, Li et al., 2018*). These findings are important as they contrast with studies of civilian polymicrobial wound infections where *Enterococcus spp.* are detected at lower rates (*Rajkumari, Mathur et al., 2014*). The next steps involve assessing strain-specific clinical outcomes and examining the interaction of *Enterococcus spp.* with other wound pathogens.

As *E. coli* is a frequent colonizing organism, as well as an infecting organism among wounded warriors, it has also been examined. Over a two-year period, 80% and 57% of infecting and colonizing *E. coli* isolates recovered from TIDOS subjects produced Extended Spectrum Beta-Lactamases (ESBL), respectively; ESBL confers resistance to certain broad-spectrum antibiotics and its presence helps determine a proper medical course of action. The isolated organisms were also genetically "fingerprinted" with pulsed-field gel electrophoresis. The analysis found a large variety in genetic diversity with little overlap when isolates were compared among the study years, combat zones, and hospitals, so there is not a single source or species that might be addressed by a standard intervention. Even among patients with a serial collection of isolates, there were changes in the genetic profiles and ESBL classification, suggesting that the same patient could be infected or colonized anew multiple times during treatment (*Mende, Beckius et al., 2014*).

An analysis examining characteristics and outcomes of *P. aeruginosa* infections among wounded warriors (90% with blast trauma) was recently completed. All patients with MDR *P. aeruginosa* infections sustained blast injuries; however, the occurrence of blast trauma was not associated with longer hospitalization (*Ford, Mende et al., 2018*). An analysis examining infections with a frequently antibiotic-resistant pathogen, *Stenotrophomonas maltophilia*, has also been completed and an analysis examining infections with *Klebsiella spp.* is nearing completion. Biofilm formation is another area under analysis to evaluate the impact of biofilm in relation to clinical outcomes (*Akers, Mende et al., 2014*).

The Importance of Follow-up on Patient Well-being

The first reports of the TIDOS DoD and VA cohort highlighted the importance of extended follow-up beyond the early post-injury period (*McDonald, Liang et al., 2018, Tribble, Krauss et al., 2018*). Approximately one-third of cohort enrollees were diagnosed with new trauma-related infections following discharge from the hospital (*McDonald, Liang et al., 2018, Tribble,*

Photo credit (opposite page): Master Sgt. Carlotta Holley/U.S. Air Force

Krauss et al., 2018). Among subjects who were diagnosed with an infection during the initial hospitalization, 45% developed a new infection following hospital discharge. Furthermore, 24% of individuals who never had an infection during the initial hospitalization were diagnosed with an infection after hospital discharge. Extremity wound infections contributed the greatest amount to the infection burden both during the initial hospitalization, as well the follow-up. Sustaining a blast injury was associated with risk of developing an extremity wound infection diagnosed during follow-up in a univariate model. Independent predictors for developing an extremity wound infection during follow-up included having an amputation (three times more likely), open fracture (four times more likely), and being diagnosed with an extremity wound infection during the initial hospitalization (two times more likely) (*Tribble, Krauss et al., 2018*). Among Veterans, the median time from hospital discharge to diagnosis of any new infection (Figure 5-4) was 88 days. In general, the likelihood of the patients developing an infection was the greatest in the first year following hospital discharge (*McDonald, Liang et al., 2018*).

Upcoming analyses will examine infection risk with regard to specific injury patterns. In addition, the St. Louis VA has collected data from patients included in the Trauma-Associated Osteomyelitis study with follow-up extending out to 10 years for a number of the subjects. Analysis of these data to evaluate the ongoing osteomyelitis risk is forthcoming. Lastly, information on social and mental well-being (*e.g.*, relationship status, alcohol/opioid abuse, and mental health diagnosis) of Veterans has been collected and analyses will be conducted to assess whether well-being is affected by the occurrence of infections or vice versa.

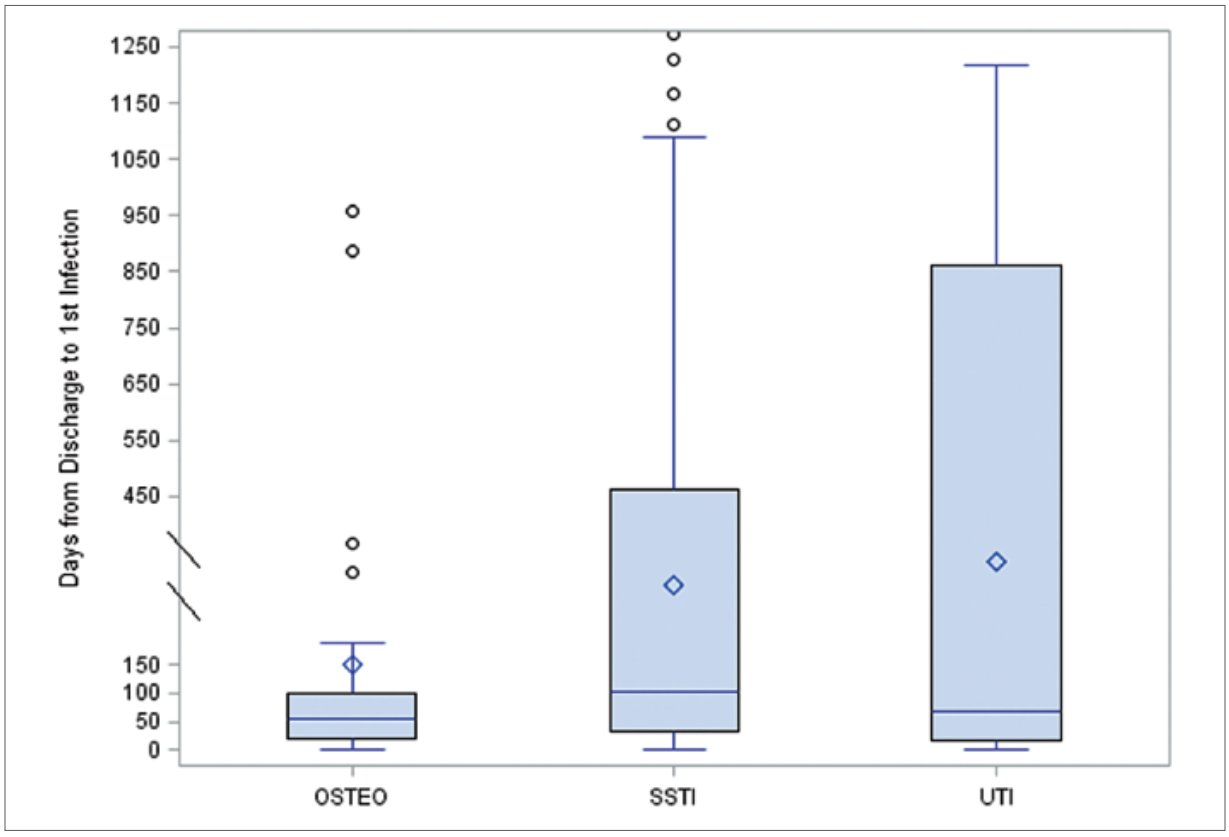


FIGURE 5-4: Time in days post-hospital discharge, to new infection related to traumatic injury. **Left:** osteomyelitis. **Center:** skin and soft-tissue infection. **Right:** urinary tract infection. *Figure is reprinted with permission of Oxford Academic Press.* (*McDonald, Liang et al., 2018*)

Photo credit: Spc. Brandon Evans/ U.S. Army

Improving Clinical Practice Guidelines

Although the improved rates of survival from serious combat trauma are generally attributed to better personal protective equipment, tourniquet use, new medications, and improvements in casualty care technology, the establishment of the DoD JTS in November 2004 directly impacted combat casualty care through implementation of multiple performance improvement initiatives at combat care facilities and dissemination of clinical practice guidelines (*Eastridge, Jenkins et al., 2006*). The JTS evidence-based clinical practice guidelines for prevention of infections following combat-related injuries (first published in 2008 and revised in 2011 and 2016) emphasized infection control, early wound care, and post-injury antibiotic prophylaxis (*Hospenthal, Murray et al., 2008, Hospenthal, Murray et al., 2011, Saeed, Tribble et al., 2016*). The guidelines covered the immediate care of patients while still in a combat zone through the period of medical evacuation to LRMC in Germany. As part of an effort to promote antibiotic stewardship and combat antibiotic resistance, the recommendations advocated against the use of broad-spectrum antibiotics (*Hospenthal, Murray et al., 2011, Saeed, Tribble et al., 2016*).

Data collected through TIDOS on use of antibiotics can be compared against practice guidelines. Over the years, TIDOS analyses have assessed adherence to JTS guidelines with regard to post-trauma antibiotic prophylaxis (*Tribble, Lloyd et al., 2011, Lloyd, Weintrob et al., 2014, Lloyd, Murray et al., 2017*). Findings from the first analysis demonstrate low compliance with specific injury patterns; these data were utilized by the JTS for process improvement (*Tribble, Lloyd et al., 2011*). Examination of data over five years of TIDOS showed that compliance with guideline recommendations improved in the later years. For example, use of broad-spectrum antibiotics declined for open fractures, demonstrating improved antibiotic stewardship (*Lloyd, Murray et al., 2017*).

Recent analyses have evaluated infectious outcomes based on specific post-trauma antibiotic prophylactic regimens (*Lloyd, Murray et al., 2017, Lloyd, Murray et al., 2018*). One analysis examined outcomes with open fractures based on whether they received the JTS-recommended narrow-spectrum antibiotic or both a narrow-spectrum antibiotic (*e.g.*, cefazolin) and broad-spectrum antibiotics. Although there was a moderate

decrease in the number of SSTIs, there was no benefit in reducing the rate of osteomyelitis with the addition of the broad-spectrum antibiotics (*i.e.*, aminoglycosides and fluoroquinolones). In addition, there were adverse consequences as more resistant organisms were isolated from patients who received broad-spectrum antibiotics. Taken together, these findings support the JTS recommendations of narrow-spectrum antibiotic for open fractures (*Lloyd, Murray et al., 2017*). In an analysis of civilian lower extremity fractures, a similar lack of benefit with added broad-spectrum antibiotics was reported. Specifically, the addition of a (broad-spectrum) aminoglycoside to a (narrow-spectrum) cephalosporin regimen had no benefit in reducing the rate of wound infections and was associated with an increase in acute kidney injury (*Bankhead-Kendall, Gutierrez et al., 2017*).

During the past year, an analysis focused on deep soft-tissue infections was initiated. Characteristics of patients with deep soft-tissue infections were assessed in relation to initial empiric antibiotic regimen (*i.e.*, carbapenem without vancomycin, vancomycin without carbapenem, carbapenem plus vancomycin, or only other antibiotics) with the objective of evaluating initial empiric management. In addition, comparative analyses with the United Kingdom Wound Infection Surveillance Programme are planned to determine best practices in relation to the management of trauma and blast-related infections. The result of these analyses and other future studies will also be conducted to support the development of guidelines for the treatment of trauma-related infections, including blast trauma.

Future Challenges

Modern warfare has created new challenges for military clinicians and surgeons caring for Service members with battlefield trauma. Due to the high proportion of blast trauma, battlefield wounds are complex with gross environmental contamination and a significant risk of acquiring a hospital-associated infection. Prolonged field care may also increase infection rates, with earlier onset and possibly increased severity. These infections have both short- and long-term impacts that may affect wounded warriors long past their initial hospitalization and beyond their military service.

In 2016, the DoD Blast Injury Research Program Coordinating Office (PCO) held an International State-of-the-Science Meeting on Minimizing the Impact of Wound Infections Following Blast-Related Trauma. Findings from recent analyses were presented by Trauma-Related Infections Research Area investigators with the Director of the Research Area participating on an expert panel. Following the review of the science, the expert panel produced six recommendations, with many being directly relevant to TIDOS. These recommendations, and the ways TIDOS can address them, are:

1. **Ensure that proactive plans, policies, procedures and clinical practices are in place to support and to sustain a "Learning Trauma Care System" consistent with a recent Institute of Medicine Report. One goal of this approach should be to seek to improve theater specific understanding, prevention, and treatment of wound infections following blast injuries.** Blast patients are complex in many ways and clinical research demands continual collection and analysis of data in real-time, as the TIDOS module conducts. The TIDOS group is able to provide an iterative process of implementation science focusing on JTS clinical practice guidelines and on assessing adherence to post-trauma antibiotic prophylaxis, continually providing feedback and reassessment to support theater-specific best practices.

2. **Coordinate – by DoD directive and all other appropriate regulatory mechanisms – routine research organizational support for sustained wound infection surveillance and analytical epidemiology in current and future theaters of operation. Initiate and sustain research upon entry to any theater of operations.** The TIDOS module supplements the DoD trauma registry with infection information from combat casualties, allowing for timely assessment of infection-related data, as was done regarding IFI among blast injured Soldiers and Marines supporting OEF.

3. **Develop a proactive, comprehensive research strategy relating to blast-related wound care, enhanced infection control, and optimal antimicrobial prevention and treatment strategies for coordinated implementation within current and future theaters of operation.** TIDOS analyses have been assessing outcomes in relation to antibiotic prophylaxis guideline recommendations, to support best practices. The work is being expanded through an upcoming collaboration with the United Kingdom Ministry of Defence Wound Infection Surveillance Programme.

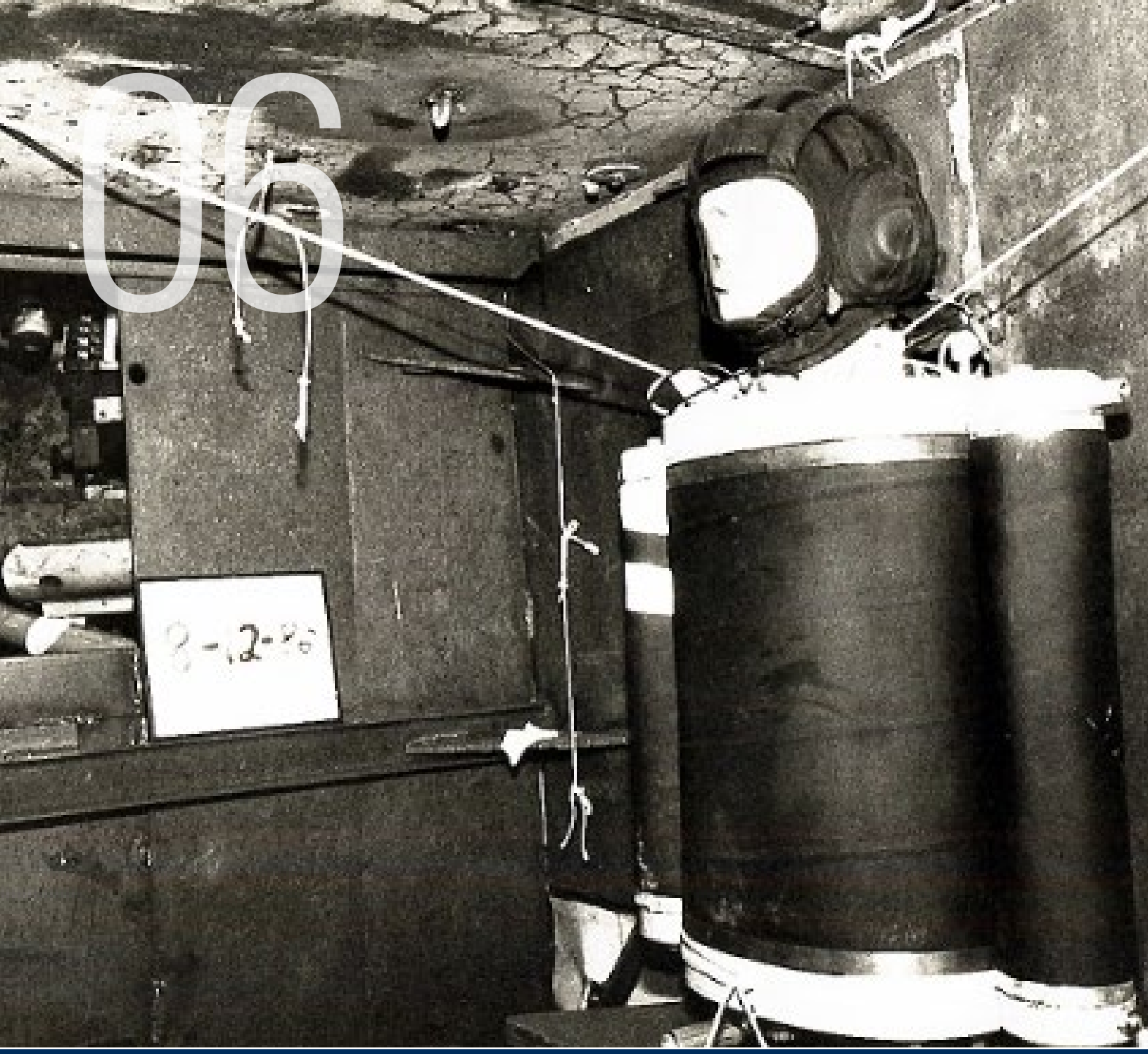
4. **Increase DoD efforts to engage and to facilitate Food and Drug Administration (FDA) involvement in meetings, strategies, and other efforts to ensure research and development of innovative, integrated therapies tackling the growing, global problem of antimicrobial drug resistance. Use FDA collaboration to facilitate industry partnerships relating to antimicrobial drug development.** TIDOS helps identify the knowledge gaps to drive product assessment and randomized controlled trials of antimicrobials.

5. **Implement a system to measure, compare, benchmark and reward compliance with existing JTS clinical practice guidelines pertaining to blast-related injury, such as improving compliance with the JTS guidelines relating to infection prevention in combat-related injuries (Clinical Practice Guideline (CPG) ID: 24) and care of patients at high risk for invasive fungal infection in war wounds (CPG: 28).** As detailed above, TIDOS has implemented many of these measures. IDCRP is also analyzing molecular diagnostic platforms for more rapid detection of fungus in tissue specimens, and refining the definitions and classifications of IFI to support JTS guidelines for IFI management.

6. **Preserve, sustain, and improve the DoD Trauma Registry and related programs (*e.g.*, TIDOS and the Military Orthopedic Trauma Registry) to improve care and to advance military-relevant research relating to wound infection after blast-related injury.** These programs all undergo iterative, critical assessment. While the enrollment for TIDOS has closed, investigators continue to utilize the data collected to conduct analyses of blast-related trauma and consequent infections. TIDOS and the DoD Trauma registry can be refined to be more agile and effective in future conflicts, in collaboration with allies, to standardize combat wound surveillance systems.

Blast-related wound infection research and clinical practice improvements continue to be needed to lessen morbidity in future conflicts. The collection of infection data through the TIDOS infectious disease module and analysis of the findings will continue to be an essential tool for these efforts and a necessary part of the treatment and mitigation of blast injury in future conflict.

Acknowledgements: Special thanks to Ms. M. Leigh Carson for her contributions to the preparation of this chapter.



06

CHAPTER 6:

PRESERVATION AND DISSEMINATION OF DOD HISTORICAL BLAST BIOEFFECTS RESEARCH DATA

The PCO initiated and is leading the effort to preserve and disseminate historical data on the biological effects of explosive blast. These data were collected at the Albuquerque Blast Test Site (BTS) on Kirkland Air Force Base (AFB), New Mexico, from 1951 to 1998. The goal of this effort is to provide broad access to these data to DoD program managers, researchers, and decision makers as well as civilian researchers engaged in understanding blast-induced injuries and developing protection technologies. Sharing the knowledge gained from this research, and making the actual data available for modern analyses, will prevent wasteful duplication of effort, conserving DoD's blast injury research resources on closing extant knowledge gaps to accelerate the development and delivery of blast injury prevention and treatment strategies for Service members.

Successful data preservation for widespread dissemination required the recovery and archiving of historical data into common forms that are complete, organized, and readily accessible; qualification of the data to ensure reliability and consistency; the population of an online data repository with interactive user tools for ongoing data collection; and the development of a web-based application that allows controlled access to the data, literature, and findings. The historical data were recovered and made searchable by the mechanism of blast injury studied: primary, secondary, tertiary, and combined threat. As the historical and contemporary blast bioeffects data are captured and made available, the scientific community will be able to test hypotheses and more robustly validate proposed models. This effort supports the EA's responsibility to disseminate information so that research programs can leverage historical knowledge and plan future research investment to address remaining knowledge gaps and avoid unnecessary and duplicative work.

Background

From 1951 until 1998, the most significant studies of the biological effects of blast outside the Eastern Bloc were conducted at the BTS on Kirtland AFB in New Mexico (*Martinez, 1999*). Thousands of experiments, on tens of thousands of animals, were conducted. The diversity of the experiments is staggering and includes blast sizes from nuclear weapon-like to occupational, animals from cattle to mice, fish, and birds, under a broad variety of conditions, and in the presence of many complicating hazards and trauma sources.

From 1951 through 1964, the BTS was funded primarily by the Atomic Energy Commission for study of the biologic effects of nuclear blast waves. Actual atomic blasts were not carried out at the BTS, but very large blasts generated by conventional explosives were used to investigate bioeffects at such high powers. This area of interest, and the accompanying studies of very large blasts, persisted until 1978 under majority funding by the Defense Atomic Support Agency (now the Defense Threat Reduction Agency). One famous product from these early years is the "Nuclear Bomb Effects Computer" (Figure 6-1); this device provided estimates for measures such as overpressure, winds, window glass speed, and cratering as a function of distance from a

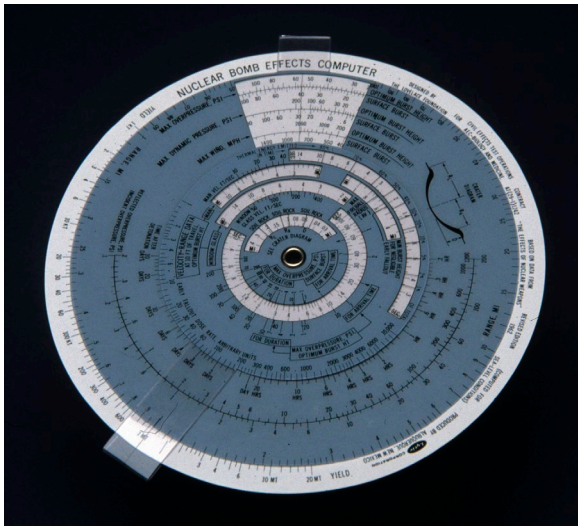


FIGURE 6-1: Nuclear Bomb Effects Computer from Smithsonian Museum of American History.

Photo credit (opposite page): PCO's Historical Blast website

nuclear blast, and includes charts indicating the probability of various medical effects. These large blasts necessitated questions of gross, dramatic effects, such as computations (*Bowen et al., 1961*) of how far individuals and equipment might expect to be thrown by an explosive blast wave (Figure 6-2). Perhaps the most frequently encountered product of the research on nonhuman animals conducted at this time were the empirical "Bowen curves" (*Bowen, Fletcher, and Richmond, 1968; Richmond et al., 1966*) for predicting injury and lethality as a function of an individual's mass, surroundings, position, blast size, and distance (Figure 6-3); these are still referenced commonly in scientific and technical studies of blast injury.

As of the late 1970's, the BTS was largely funded by the U.S. Army Medical Research and Materiel Command (USAMRMC) to investigate the biological effects of smaller and occupational blast exposure. The studies were used to develop safety standards, treatment guidance, and military tactics for minimizing damage to personnel and equipment impacted by blast events. This work includes extensive physiological studies of blast

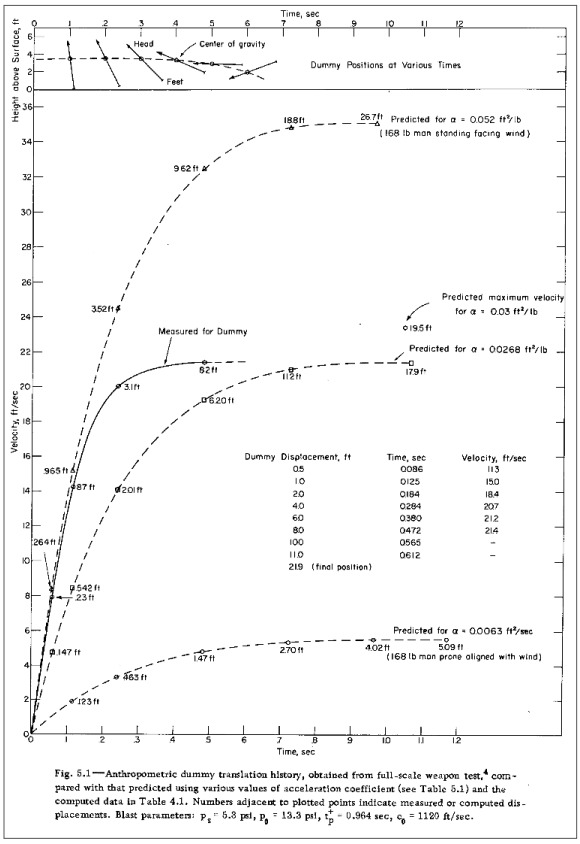


Fig. 5.1—Anthropometric dummy translation history, obtained from full-scale weapon test,[4] compared with that predicted using various values of acceleration coefficient (see Table 5.1) and the computed data in Table 4.1. Numbers adjacent to plotted points indicate measured or computed displacements. Blast parameters: p_s = 5.3 psi, p_0 = 13.3 psi, t_p^+ = 0.964 sec, c_0 = 1120 ft/sec.

FIGURE 6-2: Estimates of how far a body would be thrown by a nuclear blast, based on mannequin studies. (*Figure from PCO's Historical Blast website).*

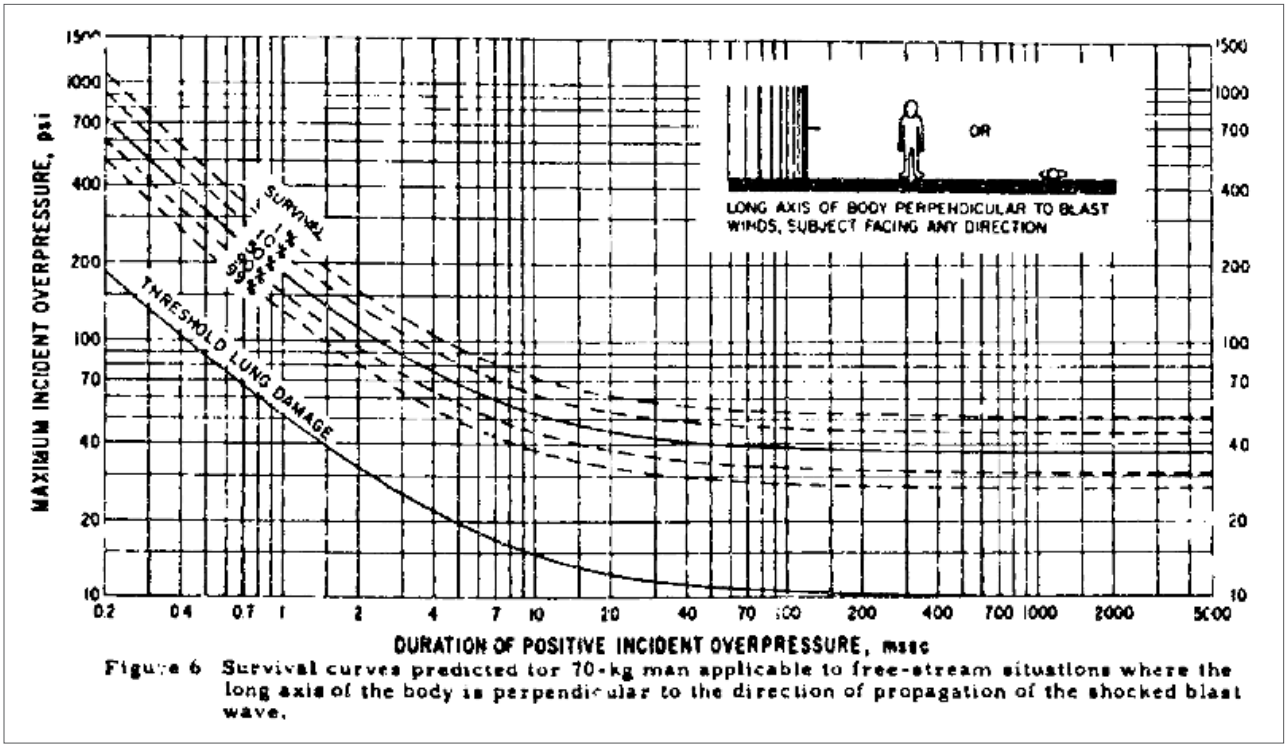


Figure 6 Survival curves predicted for 70-kg man applicable to free-stream situations where the long axis of the body is perpendicular to the direction of propagation of the shocked blast wave.

FIGURE 6-3: "Bowen curves" predicting likelihood of survival for 24 hours after a blast. (*Figure from PCO's Historical Blast website).*

effects and mitigation strategies, including, for example, an eight-year study to establish limits for heavy weapon noise, during which five large groups of volunteers were exposed to different types of impulse noise using three types of hearing protection.

The Army terminated its lease in 1998 and ceased research at the BTS. Much of this large body of work cannot be repeated, due to resource constraints, concerns about environmental toxicity, and evolving standards regarding the use of animals in research. The research and many of its conclusions are broadly unknown among current medical researchers, and moreover there has been no convenient access to these data. This lack of knowledge in the blast community falls directly within the PCO's responsibility to identify and fill knowledge gaps in blast injury research.

Historical Data Contents

Making the data available to modern researchers is complicated by the diversity of experimental configurations, data types, and storage. Even within the simple category of "shock tube experiments," in which a controlled overpressure shock wave propagates to an immobilized animal subject along a purpose-designed chamber, many different configurations of shock tubes were used, to address blasts of different intensity or duration and different positioning between subjects and blasts. To ensure future accessibility, each must be properly documented for modern researchers unfamiliar with the setup. Figure 6-4, for example, shows a classic shock tube setup used at the facility. The relevant parameters and geometry have been preserved and are conveyed to researchers accessing the historical blast data in schematic form, as in Figure 6-5.

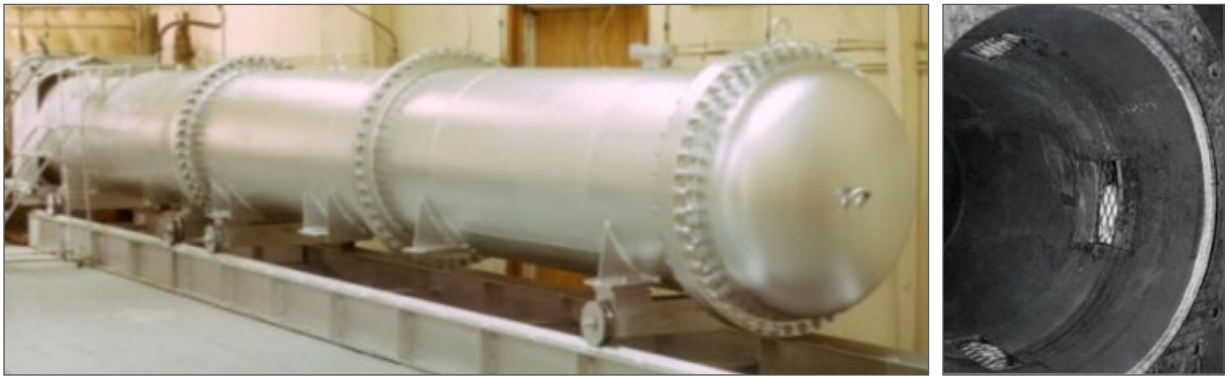


FIGURE 6-4: Example of a shock tube used for some experiments at the BTS (left); end plates have mounting locations for small animals, or restraints for larger animals (right). (*Figure from PCO's Historical Blast website).*

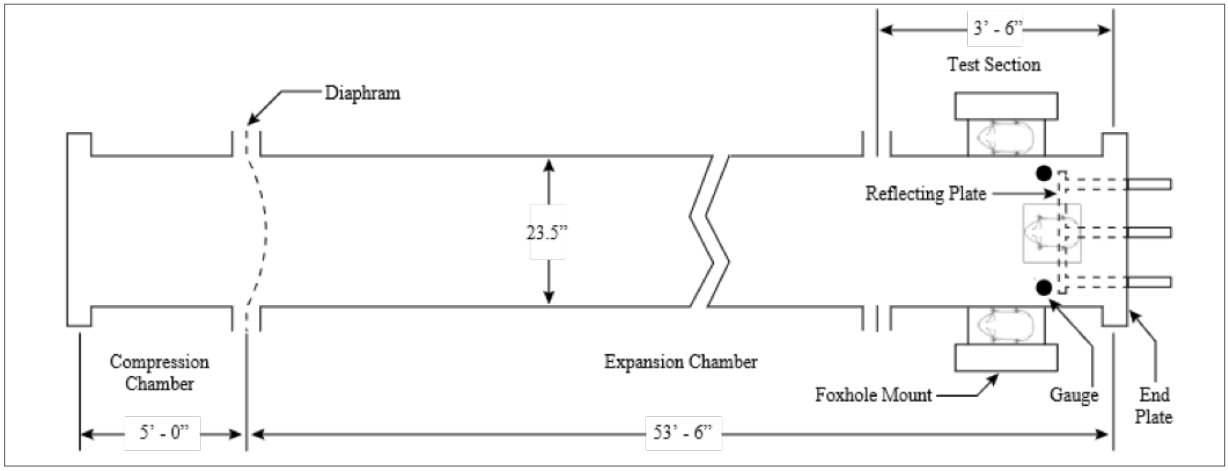


FIGURE 6-5: This example diagram from the PCO's Historical Blast website shows how the shock tube in Figure 6-4 can be rendered schematically for current-day users. (*Figure from PCO's Historical Blast website).*

Additionally, this complexity of the experimental data is compounded by the variety of experiments undertaken at the BTS that went considerably beyond shock tube experiments, to consider the effects of *e.g.,* underwater blast or radiation burns (Figure 6-6). Each experiment type requires extensive description of the setup and parameters to make the data relatable to modern studies.

The numerous, and remarkably diverse, experiments also contain studies that are directly relevant to Service member health and to combat training, tactics, and procedures (Figure 6-7). Data from the BTS are the basis for current day health and safety guidelines for preventing auditory and lung injury during heavy weapons firing. The breadth of data and the relevance to real-world situations supports the need for their preservation and dissemination.

Data Capture and Recovery

In theory, preservation is a straightforward process of archival and incorporation into a searchable database. In practice, however, the effort is much more complex. The data are, as mentioned above, quite diverse. Moreover, the types of data taken were different for different experiments, and the findings were recorded in an era before standardized digital data recording. Archiving is therefore a matter of electronically scanning and clarifying as necessary the vast amounts of handwritten logbooks and necropsy data, and determining the relationships among those data, the known experimental setups, and the publications and reports submitted to DoD.

The complexity and level of effort can be illustrated by considering a single representative study of the many studies now archived by the

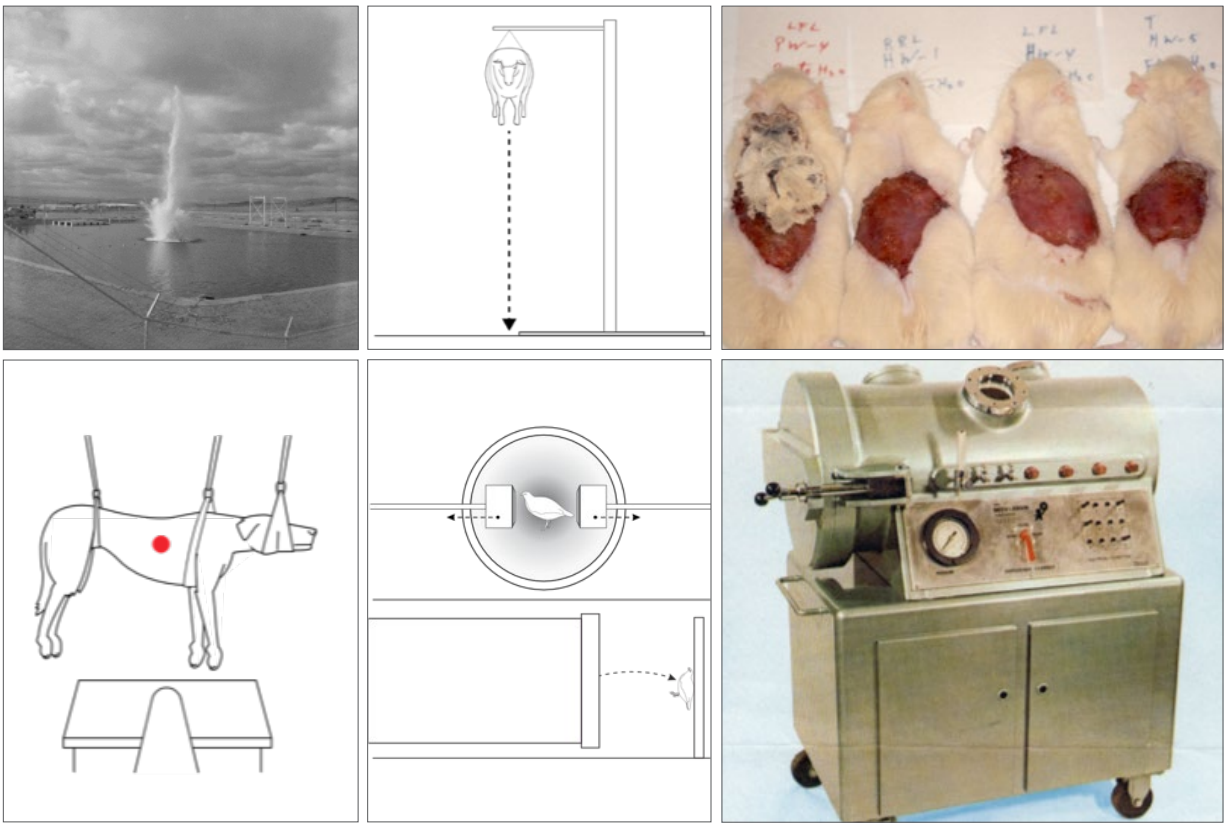


FIGURE 6-6: A small sampling of experimental diversity at the BTS includes tests of underwater blast (top left), secondary injuries from blast-driven projectiles (bottom left), tertiary injuries from falls (top center) and blasts of air (bottom center), injuries from radiation and burns (top right), and effects of recovery in hyperbaric chambers (bottom right). (*Figures from PCO's Historical Blast website).*

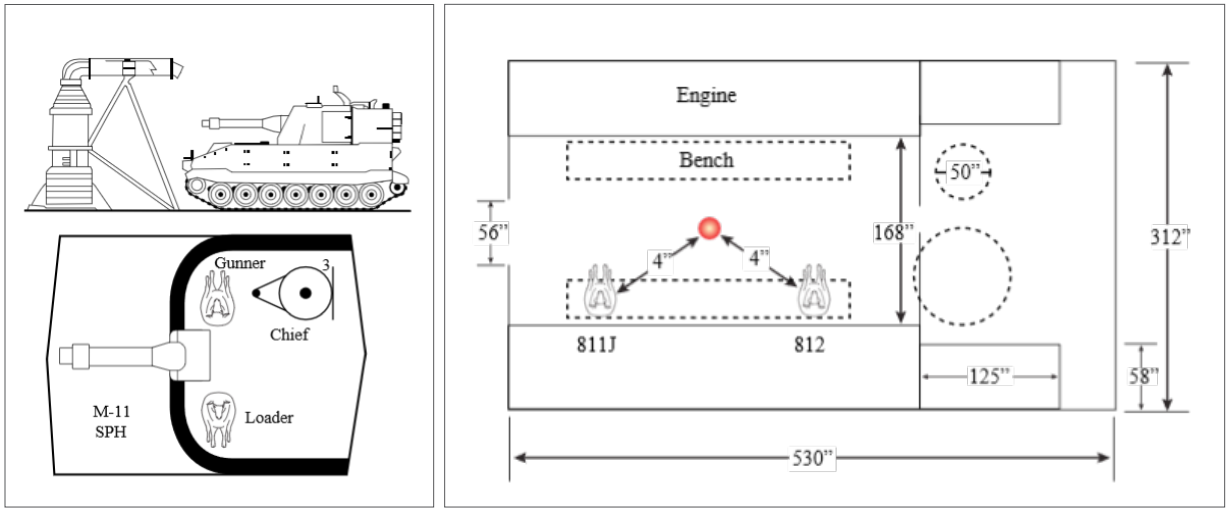


FIGURE 6-7: The BTS archive contains many tests relevant to Service member protection. Left, tests to determine acoustic damage thresholds for seating positions in an open tank. Right, interrogating blast damage in the back of an enclosed armored personnel carrier. (*Figure from PCO's Historical Blast website).*

PCO (Figure 6-8). A large collection of shock tube studies, for example, were used to develop an interspecies correlation of animal size and resistance to overpressure blasts, which could be used to extrapolate effects in humans. Data used for this exercise – which includes over 1300 tests and nearly 4200 animals – are extensive and diverse, for a single study. The figure shows some of the information for a single animal – in this case, a sheep – in a single experiment. Multiple such data must be matched to the same experimental record, which then forms part of the supporting data for a larger dataset collected to inform the broader blast injury model, and these data, in turn, are used to support multiple reports and analyses in a many-to-many relationship. Handwritten notes and graphs must be correctly aligned to experimental data, and these subsequently matched with shock tube or other experimental configurations and supported with appropriate calibration and control data, and the whole properly classified along with related records into groups supporting discrete DoD studies. This organizational effort is substantial and is maintained by the association of recovered data with appropriate metadata generated in the recovery effort, detailing the relationships among data, images, experiments, and animals.

Data Qualification

A further complication is ambiguity in, or omission of, the underlying data; data may lack essential reference points or units (as the sensor trace in Figure 6-8 contains no units of pressure nor time), or handwritten notes can be difficult to interpret. The archived data have, therefore, been subjected to rigorous quality control to verify questionable measurements and/or to augment missing values where applicable.

Photo credit: PCO's Historical Blast website

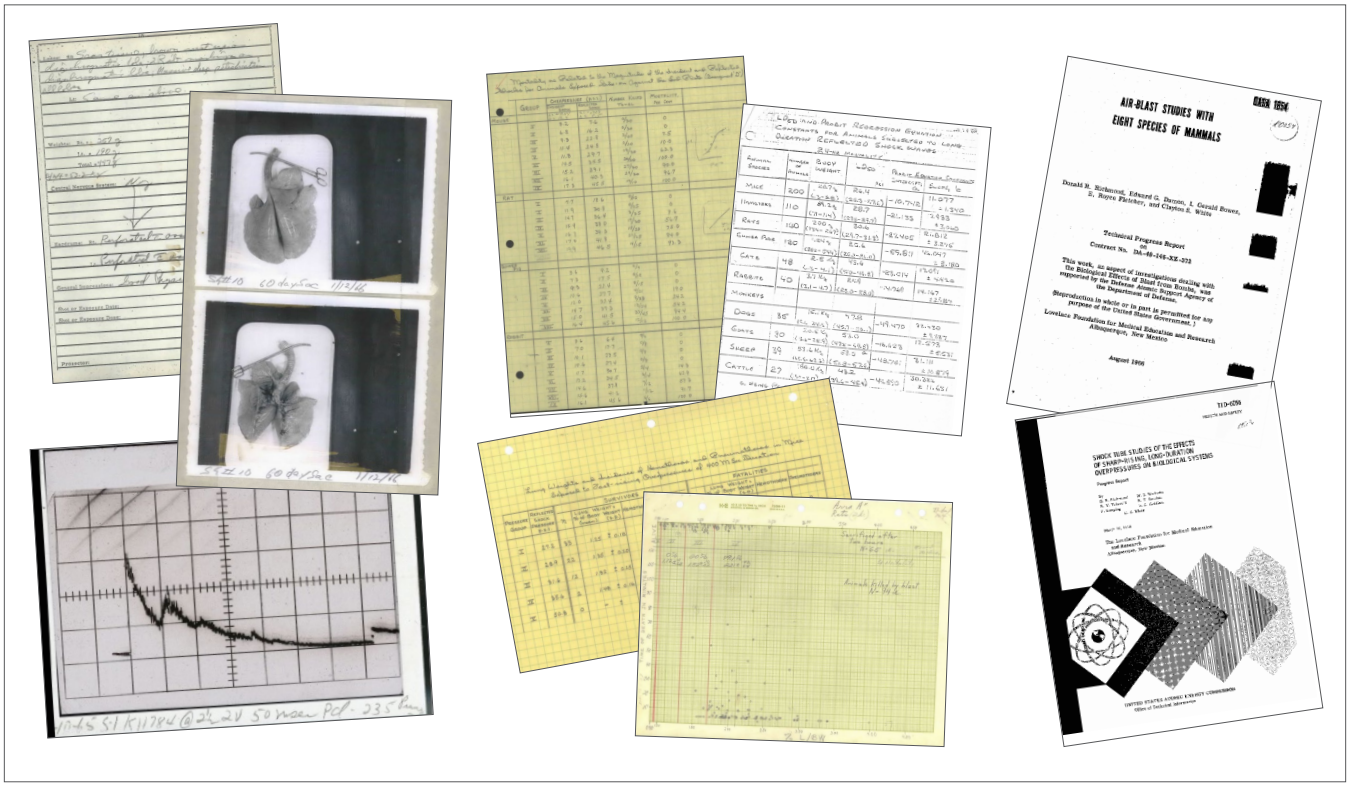
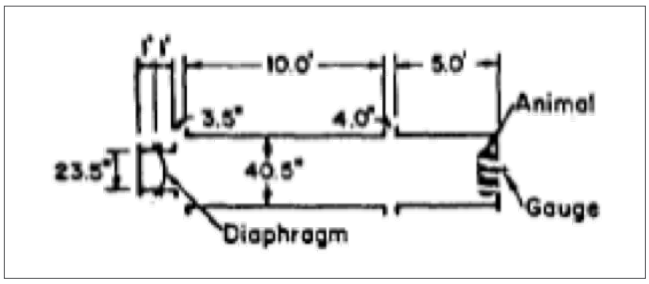
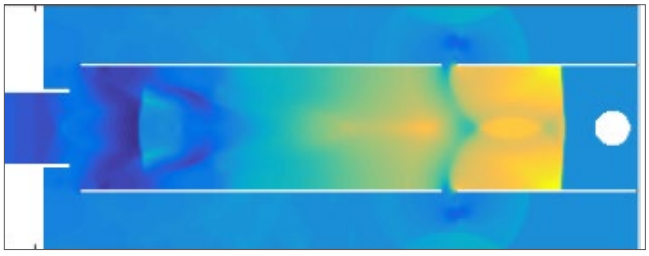
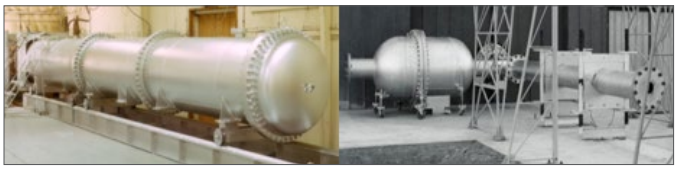


FIGURE 6-8 Associating data can be challenging. Multiple records, as with these necropsy notes and images and this sensor trace, can be associated with a single experiment on a single animal (left). These in turn become part of a larger dataset used for laboratory calculations and graphs (middle), which are in a many-to-many relationship with final reports to DoD (right). (*Figures from PCO's Historical Blast website).*



Tube L Computational Model





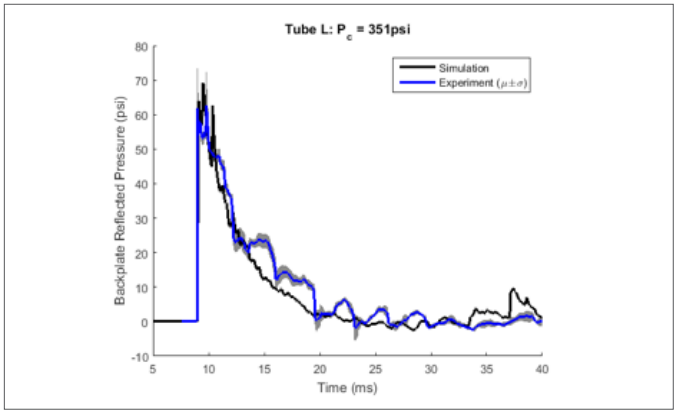


FIGURE 6-9: Diagrams and photographs from historical data (top left and right) are used to simulate pressures during blast (bottom left), and the simulation is used to scale and to validate archived sensor traces (bottom right). (*Figures from PCO's Historical Blast website).*

The contractor support for the archival effort has considerable expertise with, and experience in, blast simulation and measurement, and used computational modeling to simulate blast in the known experimental configurations. These models can be used to scale and to validate data, making them meaningful to modern researchers (Figure 6-9). While the computational approach was used for validating shock tube data, field experiments were used to validate some open-air blast data. Selected animal studies conducted in open-air blast testing were repeated by the contractor in similar configurations, but without animals and with the strategic placement of pressure gauges to validate observations made in the original data and, as with the shock tube measurements discussed above, to assign absolute values to relative pressure traces.

Web-based Data Access

The PCO has taken a lead in using web-based tools and technologies to provide access to this historical blast injury research information. The organized and validated data are available to today's community of U.S. Government-sponsored medical blast researchers through a website maintained by USAMRMC and located at https://historical.blastinjuryresearch.amedd.army.mil/.

The website confers some control over the data by giving USAMRMC the ability to grant access and preserves the relationships among the data determined during recovery and validation. Moreover, the website organizes these data along parameters meaningful to, and broadly accepted by, the modern blast injury research community. For example, the historical data

Photo credit: PCO's Historical Blast website

Photo credit: PCO's Historical Blast website

are searchable within the website by the mechanism of blast injury studied: primary, secondary, tertiary, and combined threat (Figure 6-10). Further, experimental data are grouped by type, so that the user can make a selection with the click of a pull-down menu to view experiments relevant to a particular inquiry.

The web interface also provides forms for entering new data, with guides and tools for inserting appropriate studies into the site hierarchy. These tools ensure that the database will continue to be enriched with new data, which will be immediately available as a tool to the worldwide blast research community.

Photo credit: PCO's Historical Blast website

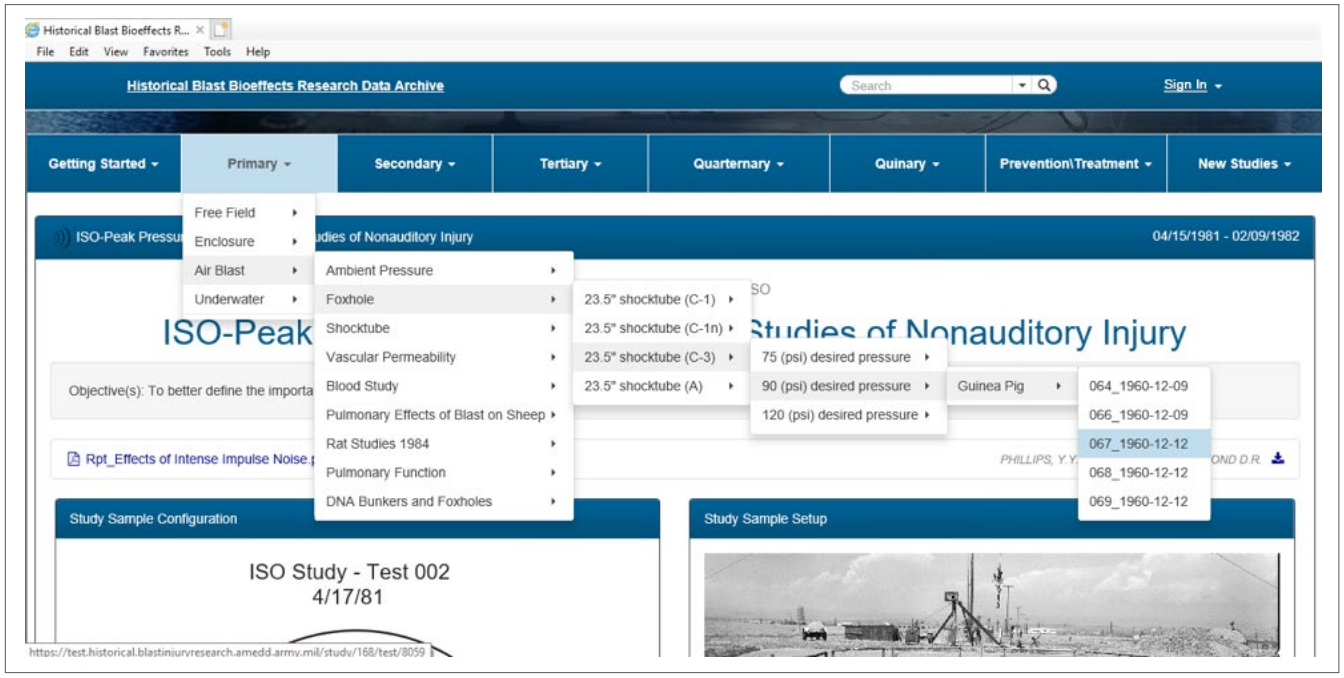


FIGURE 6-10: The historical blast website organizes information for modern researchers, so relevant experiments can be found by blast injury type, then type of blast, experimental setup, and model animal. (*Figure from PCO's Historical Blast website).*

Envisioned Uses and Way Forward

Considerable financial resources and intellectual capital were allocated to gather historical blast injury data, and their conclusions need not be limited to operational advancement and scientific publication at the time. Indeed, the experimental diversity suggests the data are relevant to many military and civilian medical applications, and their usage should therefore be maximized. At the Historical Blast Bioeffects Research Data Archive, experimental findings can be downloaded and examined such that users can gather methodological protocol measures and animal injury outcomes to determine what research gaps need to be filled with new experimentation or simulation, thus minimizing duplicative efforts and animal sacrifice. Further, these data can be used to evaluate survivability for military and civilian personnel under numerous hypothetical explosive detonation scenarios to allow for sufficient preparation and/or the development of treatment strategies for casualties. And lastly, this expansive historical blast dataset can be applied to existing research on developing heavy munitions systems that are safe for users and/or constructing or altering protective equipment to mitigate injury due to explosives.

In addition to hosting the blast historical data for reference, the website is also a portal whereby contemporary researchers can upload their more recent experimental blast data to add to the already sizable repository to facilitate data harmonization and maximize its impact to future research discoveries.

07

CHAPTER 7:

DOD BLAST INJURY RESEARCH PROGRAM ACCOMPLISHMENTS

The PCO's EA support mission is to coordinate DoD blast injury research investment and leverage expertise to develop strategies that prevent, mitigate, or treat blast injuries. To inform the EA of accomplishments throughout the blast injury research community, the PCO requested data from DoD organizations engaged in medical and nonmedical blast-related research that occurred in FY18. The PCO received responses from 96 organizations, summarized in the chapter that follows. These accomplishments are organized by the DoD Blast Injury Research Program's key program areas: Injury Prevention, Acute Treatment, and Reset. Each accomplishment adds to the knowledge base for blast injury research and refines the strategies that prevent blast injury or allow injured Service members to return to duty (RTD) and maintain an active lifestyle.

Program Area: Injury Prevention

Research on blast injury prevention considers the entire spectrum of potential injuries, from primary to quinary. The design of prevention systems requires understanding of the mechanism of injury; thus, significant research efforts are focused on replicating blast exposure conditions in the laboratory and determining blast injury mechanisms using animal and computational models. Also researchers are collating clinical and theater data to analyze blast threats and assess personal protective equipment (PPE) performance. The acquired data are being used to better refine safety thresholds for human exposure to blast, support the design of protection systems, strengthen guidelines for the safe use of weapon systems, and identify biomarkers and potential treatment targets. Findings are shared between the military and civilian research and development communities to encourage greater use and availability of protective measures against blast events in both sectors.

Injury Risk Assessment and Criteria Development

Identifying Optimal Biomechanical Metrics for Development of Human Injury Risk Curves

Human injury risk curves (IRC) for blast loading are needed to improve and assess safety in military operational environments. Biomechanical metrics from human cadaver tests can be used to develop IRCs, but the optimal metric for determining injury risk in these studies is not clear. Researchers at Medical College of Wisconsin (Milwaukee, WI) used the Brier Score Metric (BSM) to identify the metric that best describes the underlying response to injury.

To demonstrate use of BSM, the researchers developed optimal IRCs for skull fracture from head injury tests using previously published data from 12 cadaver specimens (*Yoganandan and Banerjee, 2018*). Failure force, deflection, energy, linear stiffness, and secant stiffness variables were evaluated for hierarchical relevance to determining the risk of injury. The mean magnitudes sufficient to cause skull fracture for these variables were 9168 N (force), 8.9 mm (deflection), 30.8 J (energy), 2418 N/mm (linear stiffness), and 1425 N/mm (secant stiffness). Optimal distributions and normalized confidence interval sizes were determined for each variable.

Lognormal distributions were used for all variables except failure force, for which a Weibull distribution was applied. Based on BSM scores and confidence interval tightness, failure force was the optimal metric for determining risk of skull fracture, followed by deflection and energy. Failure forces of 3687, 4734, and 9104 N were associated with 5, 10, and 50 percent probabilities of skull fracture, respectively.

Photo credit (opposite page): Pfc. Derek L. Kuhn/U.S. Army

Using BSM-identified optimal metrics to develop IRCs will lead to better correlates of injury from mechanical loads in computational models, and it will have greater power and robustness in predicting Service member injury.

This effort was supported by MOMRP/JPC-5.

Lower Than Expected Levels of Cochlear Exposure Derived from Cadaveric Studies Lead to Refinement of Human Transfer Functions for Predicting Auditory Injury Risk

Auditory injury is a leading cause of medical referrals for Service members, and propagation of blast waves through the ear could exacerbate brain injury. Researchers have previously relied on models such as the Auditory Hazard Assessment Algorithm in Humans (AHAAH) model to predict the amount of auditory hazard after blast, however these models have limitations especially in large amplitude impulses.

Researchers at Applied Research Associates, Inc. (Littleton, CO) and the University of Colorado School of Medicine (Aurora, CO) previously developed a chinchilla-to-human transfer function to determine the human-equivalent of the blast exposure that leads to permanent hearing loss in chinchilla. The investigators are currently refining the AHAAH in multiple model systems to test which protective systems best mitigate auditory injury.

Recently, the team has published work on human cadaveric head experiments to better measure the response of auditory system components involved in the transmission of acoustic exposure (*Greene, et al., 2018*). Pressure sensors were placed in the ear canal, middle ear, and inner ear to determine pressure transmission (n = 16 ears). They found that the magnitudes of middle-ear transfer functions at high intensity impulses were lower than expected, meaning transfer functions determined from mild-to-moderate intensity pulses should not be used to extrapolate exposure from higher impulses. These data will be used to refine models predicting auditory risk.

This effort was managed by CDMRP with support and program oversight by MOMRP/JPC-5.

Health Hazard Analyses and Blast Overpressure Assessments Performed During the Acquisition of Army Weapon Systems

The U.S. Army Public Health Center (USAPHC; Aberdeen Proving Ground, MD) performed Blast Overpressure (BOP) Analyses on six weapon systems during FY18. These BOP Analyses support the Health Hazard Assessments (HHAs) associated with each weapon system. The following weapon systems were assessed to determine their BOP effects: the XM1287 Armored Multi-Purpose Vehicle Mortar Carrier, the M821A3E1 81 Millimeter (mm) Enhanced Mortar Cartridge, the Lightweight Multi-Role Anti-Armor Anti-Personnel Weapon System M3E1 Carl Gustaf 84mm Recoilless Rifle (Figure 7-1), the XM111 and XM112 Offensive Hand Grenades, and the XM1147 120mm Advanced Multi-Purpose Cartridge. Each of these weapon systems or cartridges provides a unique capability to produce large blast events designed to enhance the lethality of warfighters and to protect them during combat.

To determine the blast to which Soldiers using these systems would be exposed, BOP data were collected for each weapon system. Data were collected at Yuma Test Center (YTC; Yuma, AZ) and U.S. Army Aberdeen Test Center (ATC; Aberdeen Proving Ground, MD) with blast test devices at crew positions simulating the location of personnel during firing events. Different conditions were tested for each weapon system using variations in charge, elevation, hatch and ramp configuration, zone, line of fire, round conditioning temperature, firing postures, cartridge types, and location of the blast event depending on the properties of the weapon system.

These data were then sent to the USAPHC and analyzed using the BOP-HHA software version 2.1. This software was developed by the USAMRMC

FIGURE 7-1: **M3 Multi-Role Anti-Armor Anti-Personnel Weapon System (MAAWS) M3E1 Carl Gustaf 84mm Recoilless Rifle**

under a contract with JAYCOR Corporation (now L-3 Technologies). It uses an algorithm based on a biomechanical model of the thorax that calculates the amount of "push," or mechanical work, imparted to the thorax by a blast pressure wave. The BOP-HHA algorithm uses the calculated work values and information about injuries from over 1,000 blast-exposed animal specimens to estimate lung injury risk and to determine the allowable number of rounds (ANORs) to which a Soldier can be exposed in a single 24-hour period without damaging one percent or more of the surface area of her or his lungs. The ANOR, as well as quantitative probabilities of lung injury for all lung injury severity levels, were determined for the conditions tested by ATC/YTC for each crew position specific to each weapon system. The hazard probabilities and severities were used to assign Risk Assessment Codes to each weapon system for BOP exposure.

BOP Analyses are published by the USAPHC in the HHA Reports used by Safety and Occupational Health professionals during the acquisition process. The results of BOP analyses are included in standard operating procedures that commanders use to make decisions about blast exposures when planning missions.

This effort was supported by USAMRMC, YTC, and ATC.

The Role of Reflexive Middle-ear Muscle Contractions in Damage-risk Criteria for Impulsive Noise

Researchers at the U.S. Army Aeromedical Research Laboratory (USAARL; Fort Rucker, AL) conducted a study to identify the impact of acoustic forces (impulses) on middle-ear muscle contractions (MEMC) in response to anticipated and unanticipated acoustic impulses to inform efforts to develop and revise damage risk criteria for exposure to loud noises such as those experienced by users of military and civilian weapon systems. Data analyses focused on (1) determination of reflexive MEMC resulting from acoustic and non-acoustic tasks; (2) development of models that identify correlations between acoustic signals and reflex MEMC; and (3) identification and evaluation of concomitant muscle activities that could interfere with detection of reflexive and conditioned MEMC. Results indicate that non-acoustic tasks are most likely to produce reflexive MEMC and that brief acoustic tasks are not common enough to include as a protective factor in damage-risk criteria for impulsive noise.

Improvements in accuracy of damage risk criteria will benefit warfighters and other personnel exposed to impulsive sound. In addition, these criteria could inform the evaluation of damage caused by impulsive noise (*e.g.*, impacts, impulses) for firearm users and other high-level industrial noises.

This effort was managed by CDMRP with support and program oversight by MOMRP/JPC-5.

Epidemiologic Studies of Occupational Blast Exposure

Occupational blast exposure denotes repeated exposures to low-level blast events that occur as part of training and operational activities experienced by personnel in designated roles in the military and law enforcement such as indirect fires (*e.g.*, artillery, mortar), explosive breaching, and anti-armor weapon operation. These exposures are not known to result in acute diagnosable injury, but there has been concern for negative neurologic effects that may be cumulative in nature.

On this hypothesis, two independent teams at Walter Reed Army Institute of Research (WRAIR; Silver Spring, MD) and the Naval Health Research Center (NHRC; San Diego, CA) analyzed archival medical records from more than 275,000 Service members to identify biomedical risks that may present clinically. Each team used military occupational specialty (MOS) codes as a proxy for longitudinal surveillance measurements of chronic exposure.

One research team assessed effects on self-reported symptomology in Post-Deployment Health Assessment (PDHA) records for active duty enlisted Marines, and the other research team examined standard of care diagnosis codes related to neurologic injury for active duty Soldiers. Each study showed evidence for negative effects in hearing ability for these exposed populations, but only the analysis of the PDHA data found evidence for other neurologic risk.

These findings suggest that (1) self-reported symptomology (PDHA) may be a more sensitive measure than standard of care diagnosis codes, and (2) criteria for entries in standard of care medical records may exceed the degree of symptomology present or be limited to those who seek medical attention. Thus, hypothesized risks from occupational exposure may manifest as symptomology not visible in the current medical system. The epidemiological evidence described here may indicate near term opportunities to guide efforts to reduce hearing ability risk among exposed Service members.

This effort was supported by CCCRP/JPC-6.

Using the Biodynamic Data Resource to Derive Injury Risk Curves Under Different Impact Load Vectors

Biomechanical experiments replicating field injuries are necessary to determine injury mechanisms and tolerances in terms of variables like acceleration. Studies of non-contact impact acceleration tolerance using human volunteers and nonhuman primates (NHP) were conducted from 1973 to 1989 at the Naval Biodynamics Research Laboratory. The Biodynamic Data Resource (BDR), a database from these tests, is kept by the U.S. Army Aeromedical Research Laboratory (USAARL). Researchers at the Medical College of Wisconsin (Milwaukee, WI) and USAARL collaborated to analyze the NHP data in the BDR and develop Injury Risk Curves (IRC) for non-contact impact acceleration.

Data from tests in the +Gz loading direction were included; this vector is associated with impacts such as those from underbody blasts. Over 400 tests with NHPs were conducted, but only those with accelerations at potentially injurious levels (38 g or greater) were included in this analysis (n = 27) (*Abraczinskas et al., 2018*). Medical records were analyzed to determine whether cardiovascular, thoracic, or cervical injuries occurred, and IRCs were developed with acceleration as the response variable.

Photo credit: Lance Cpl. Jesus Sepulveda Torre/U.S. Marine Corps

Of the 27 included tests, 11 were non-injurious and 16 were injurious. The primary injuries were thoracic injuries, followed by cardiovascular and cervical injuries. Mean acceleration magnitudes of 42, 55, and 87 g were associated with 25, 50, and 95 percent probabilities of injury, respectively. The quality indexes were in the good to fair category at these risk levels. With the use of appropriate scaling techniques, these acceleration thresholds could be comparable to human tolerances for +Gz loading, which is important for designing protection from underbody blasts while in a vehicle.

This effort was supported by MOMRP/JPC-5.

Using Novel Statistical Modeling Techniques to Develop Age-specific Neck Injury Risk Curves for Women

Injury tolerances and specifications for injury assessments are based on data from human cadavers and are targeted to the male population. Anatomical differences exist between men's and women's spines, and the intrinsic load-paths or load-sharing among their components are also different. With the increasing role of women in military operational environments, female-specific Injury Risk Curves (IRC) are needed to improve and assess safety of female Service members.

Researchers at the Medical College of Wisconsin (Milwaukee, WI) developed IRCs to support this goal (*Yoganandan et al., 2018*). Head impact tests using upright and inverted head-spine preparations from female cadavers (n = 20, age range 29–95) were conducted with data gathered on injury and non-injury producing forces. IRCs were derived for females of 35, 45, and 63 years of age. These IRCs indicate increasing injury probability with age at a given force. A comparison of the female-specific IRCs for 63 years of age (the mean in this study) with male-specific IRCs for that age from a previous cadaver-based study demonstrates that female-based IRCs are left-shifted; that is, female spine tolerance to injury from head impact loading is lower than male spine tolerance at all impact forces.

These female-specific IRCs will assist in the development of Injury Assessment Reference Curves or Injury Assessment Reference Values at pre-chosen risk levels as design and evaluation tools for injury prevention. They will be also useful in the validation and application of finite element models of female necks for injury prediction.

This effort was managed by CDMRP with support and program oversight by MOMRP/JPC-5.

CARE Consortium: Providing Evidence Against Hiding mTBI symptoms

The National Collegiate Athletic Association (NCAA)-Department of Defense (DoD) Grand Alliance: Concussion Assessment, Research, and Education (CARE) Consortium aims to better understand the development of injury and trajectory of recovery from concussion. The CARE Consortium has consented over 37,000 student athletes and service academy cadets at 30 sites. The Consortium has two study arms, the first being a clinical study focused on examining the natural history of concussion with a multisite, longitudinal investigation of concussive and repetitive head impacts. The second arm builds upon the first arm, with a clinical study allowing for more advanced research projects, such as testing impact sensor technologies, studying potential biomarkers, and evaluating concussion with advanced neuroimaging.

One of the high-impact findings from FY18 demonstrated that an immediate reduction of activity following concussion lead to faster recovery (*Asken et al., 2018*). From a dataset of 506 college athletes with diagnosed sport-related concussions, individuals were classified as immediate removal from activity (I-RFA) or delayed removal from activity (D-RFA). The I-RFA group included those who, according to the postinjury clinical reporting form, immediately reported their injury and were then immediately removed from play. The D-RFA group included those who did not immediately report their injury and/or were not immediately removed from play. Those in the I-RFA group lost significantly fewer days of activity because of sport-related concussion than those in the D-RFA group—approximately three fewer days. Those in the I-RFA group were also significantly less likely than those in the D-RFA group to have a recovery period lasting longer than 14 days, and their self-reported symptoms were less severe.

Other highlights from the CARE Consortium in 2018 include: significantly higher mean diffusivity in white matter tracts of concussed American football players than in the non-concussed, with axial diffusivity significantly correlating with acute symptomology (*Mustafi et al., 2018*); a lack of correlation between head impact biomechanics and symptomology (*Rowson et al., 2018*); and an intensifying effect of a history of anxiety, depression, or anxiety with depression on the number and severity of reported concussion symptoms (*Weber et al., 2018*).

This effort was managed by CDMRP with support from PH/TBIRP and programmatic oversight by CCCRP/JPC-6.

Hearing Loss and Protection

The Impact of Biological Sex on the Response to Noise and Otoprotective Therapies Against Acoustic Injury in Mice

Researchers at the University of Maryland-Baltimore (Baltimore, MD) conducted a study to compare the impact of suberoylanilide hydroxamic acid (SAHA), a drug that protects against noise-induced hearing loss (NIHL), on male and female mice exposed to noise trauma. Mice of both sexes were exposed to two hours of noise at 101 decibels. The animals were injected with SAHA in the body cavity three days before and two hours after noise exposure. Electrical auditory responses to tones at different radio frequencies were recorded prior to and following noise exposure to determine temporary and permanent shifts in hearing

thresholds. It was determined that female mice had smaller shifts in temporary and permanent hearing thresholds compared to males (*Milon et al., 2018*). When treated with SAHA, males experienced greater hearing protection compared to females. However, the protective effect of SAHA was smaller than the protective effect of sex (*i.e.*, being female provided more protection than using SAHA). This difference could be due to the level and activity of sex specific hormones such as estrogen. These findings support the necessity of examining the effects of noise-induced hearing loss NIHL therapies in different sexes and the potential of targeting sex-specific hormones to treat or prevent NIHL.

This effort was managed by CDMRP with support from PH/TBIRP and programmatic oversight by CRMRP/JPC-8.

Effects of Blast Injury on Hearing in a Screened Military Population Using the Blast-related Auditory Injury Database (BRAID)

During deployment, exposure to dangerous levels of combat noise, such as blast, may lead to impairments in sound recognition and communication, thereby reducing situational awareness. In addition, blast injury has been linked to hearing loss. In a recent study, the Naval Health Research Center (NHRC) investigated predictors of hearing loss among those with blast injury using data from the Blast-Related Auditory Injury Database (BRAID).

The study analyzed data from individuals that had taken a qualified hearing test within a year prior to, and following, injury (n = 1,574). Two groups were created, blast-related injury (BRI) and non-blast-related injury (NBRI). The results showed that those who sustained a blast injury were more likely to experience post-injury hearing loss (odds ratio [OR]: 2.21; 95 percent confidence interval [CI]: 1.42, 3.44), low-frequency hearing loss (OR: 1.95; 95 percent CI: 1.01, 3.78), high-frequency hearing loss (OR: 2.45; 95 percent CI: 1.43, 4.20), and reduced hearing sensitivity compared with a non-blast injury (NBRI) group (*Joseph et al., 2018*). It is estimated that approximately 63 percent of the risk for low frequency and high frequency hearing loss in deployed Service members with blast injuries could be attributed to the BRI event. NHRC's research with the BRAID will help identify at-risk populations for early intervention and hearing loss prevention, develop supportive policies and best practice guidelines for clinicians, and allocate appropriate funds and resources.

This effort was managed by CDMRP with support from PH/TBIRP and programmatic oversight by CRMRP/JPC-8.

Inner Ear and Auditory Cortex Responses to Blast Shockwave Exposure

Hearing loss is one of the most common disabilities in military personnel exposed to blast shockwaves. To better understand the pathological processes underlying the injury, investigators at Walter Reed Army Institute of Research (Silver Spring, MD) evaluated changes in ear structures, gene activity in the cochlea (the structure that senses and converts sound waves into electrical signals), and neuronal structures in the auditory region of the brain (auditory cortex) using a rodent model of blast injury. Anesthetized mice and rats were exposed to blast overpressure using an Advanced Blast Simulator resulting in auditory deficits observed across the entire acoustic frequency spectrum. Perforation of the eardrum and hemorrhage in the middle and inner ear were observed at one- and seven-days post-injury. Most were healed at 28 days after injury.

In the acute phase post-injury (one day), over 1000 genes displayed different activity in the cochlea. In the chronic phase post-injury (one month), activity only differed in 48 genes. These genes play a role in several biological processes including nervous system development and cell signaling. Genes with altered activity in the

chronic phase were primarily related to immune system activity.

Changes in the signaling surfaces between neurons (synapses) were also evaluated. Changes in neuronal structure indicative of stronger connections between neurons (increased dendrite density) were observed on auditory cortex neurons in the acute phase after blast exposure. The shape and number of dendrites correlated with the strength of the signal transmission.

Taken together, these findings reveal the impact of blast shockwave injury to the ear and hearing-related neural activities that affect auditory function and govern regenerative processes. Further study of altered gene activity may provide insights into new methods for treating or preventing blast-induced auditory deficits.

This effort was supported by USAMRMC.

Hearing Protection Technology and Education to Prevent Auditory Injury when using MAAWS

The Health Hazard Assessment (HHA) outlines hearing protection requirements for specific weapons including the M3 Multipurpose Anti-Tank and Anti-Personnel Weapons System (MAAWS) which can generate noise over 185 peak decibels (dBP) and requires the use of earplugs (earpro) and, in some, cases earmuffs as well. The Auditory Hazard Assessment Algorithm for Humans (AHAAH) model predicts the risk of hearing loss when the HHA guidelines are followed. Researchers at the Army Hearing Division (AHD) of the Army Public Health Center (APHC) conducted a set of field studies to assess the effectiveness of current guidelines to prevent auditory injury. The initial study conducted at Joint Base Elmendorf-Richardson (JBER; Alaska) documented hearing protection training and use. It was determined that hearing protection training, sizing, fit, use, and wear were not sufficient. Soldiers using the MAAWS had a temporary (18 percent) and permanent (12 percent) decrease in auditory sensitivity, which is significantly higher than the auditory injuries incidence (five percent) predicted by the AHAAH model.

These findings led to a pilot project aimed to reduce auditory injuries by providing better education on hearing health and protection sizing, fit, and use. Additionally, study participants were provided with a "FitCheck" technology which verifies the user has adequately donned their earplugs. No Soldiers experienced temporary and/or permanent hearing loss after receiving the hearing protection training and technology.

Following these improvements, the APHC AHD evaluated the feasibility and effectiveness of the "FitCheck" technology and hearing health education to prevent auditory injury when using MAAWS. Soldiers at the Joint Readiness Training Center (Ft Polk, LA) and Ft Drum, NY were included in the study. Early findings suggest that more than five percent of Soldiers experienced auditory injuries while wearing earpro, hearing protection worn by MAAWS users. The team is currently evaluating factors that may impact hearing protection (*e.g.*, dislodgment of earmuffs).

This effort has led to changes in the MAAWS training manual. Training now includes hearing protection health education, annual "FitCheck" measurements, semi-annual audiometric monitoring, and a request for a similar study for firing other overpressure weapons.

This effort was supported by Army Hearing Division Health Hazard Assessment Division.

P13 Peptide as Ear Drops Against Auditory Dysfunction Resulting from Occupational Level Repeated Blast Exposures

Repeated low-level blast exposures during military training are implicated in auditory

dysfunctions. However, no effective treatment strategies have been developed. Anti-inflammatory peptide, P13, generated by 13Therapeutics (Portland, OR) has shown significant promise against noise-induced hearing impairments in mice. Researchers at Walter Reed Army Institute of Research (WRAIR; Silver Spring, MD) are planning to test the efficacy of topical administration of P13 as ear drops for protection against occupational level blast-induced auditory dysfunctions using an advanced blast simulator in validated pre-clinical models. Previous work by 13Therapeutics has revealed that P13 applied topically crosses the intact eardrum into the inner ear to prevent hearing impairment after noise exposure. These findings reveal the potential of P13 as a non-invasive therapeutic strategy against blast-induced auditory dysfunctions in Service members.

This effort was managed by CDMRP with support and program oversight by MOMRP/JPC-5.

Repetitive Blast Exposure

Human Exposure to Occupational Repetitive Blast: Immediate, Acute, and Longitudinal Effects

The Walter Reed Army Institute of Research (WRAIR; Silver Spring, MD) is conducting multiple studies in conjunction with operational training exercises to support evidence-based decisions regarding repeated low-level blast exposure effects, monitoring feasibility, and health risk assessment. These studies characterize personnel exposure to low (≤4 psi) and moderate overpressure (4–8 psi) from a variety of weapon systems (*e.g.*, 50 caliber rifle, Gustaf recoilless rifle, hand grenades) and tactical scenarios (*e.g.*, shotgun breaching, heavy wall breaching). Researchers are investigating neurocognitive performance, symptom reporting, and physiological responses including blood-based biomarkers for neurotrauma, epigenetics, eye-tracking, and balance.

Data are collected immediately following blast exposure, at end of the day, and, where available, longitudinally across 2–3 years from a cadre of instructors. Recruitment is active with 337 subjects to date at 13 sites, including ongoing longitudinal data for 39 subjects, with 15 visits over 18 months completed. Results from these investigations indicate that current guidelines for minimum safe distances are often inaccurate in complex environments, as overpressure exposures have consistently exceeded the 4 psi incident safety threshold prescribed by U.S. Army doctrine across the studied weapons systems. Cognitive deficits (*i.e.*, 30 percent degradation in Simple Reaction Time (SRT; a component of the Defense Automated Neurobehavioral Assessment)) identified immediately after blast exposure were associated with higher peak overpressures, with those presenting SRT deficits having significantly higher single and cumulative average overpressure exposures than those not presenting deficits. Longitudinal effects have not been observed to date, but studies are ongoing.

Additional experiments include collecting data from biofidelic human head and brain surrogates equipped with interior and exterior pressure sensors and cell packs of live mouse neurons; this work examines the biomechanical effects of blast loading on the head and brain (*e.g.*, pressure, strain, multi-component displacement, acceleration, cellular function). Surrogate brains exposed to 8 and 12 psi incident pressures had 50 and 60 percent reductions in metabolic activity, respectively. Overall, this program provides critical information for understanding occupational blast exposure and associated neurological and physiological effects. Results are an asset for risk/benefit assessment and aid in developing detection and mitigation strategies for Service members in combat and training environments.

This effort was supported by MOMRP/JPC-5.

The Development of Exposure Standards for Repeated Blast Exposures

A collaborative team from institutions including Walter Reed Army Institute of Research (WRAIR; Silver Spring, MD); Naval Medical Research Center (NMRC; Silver Spring, MD); National Institutes of Health (NIH; Bethesda, MD); and the University of Virginia (UVA; Charlottesville, VA) are conducting a multi-year, multi-institutional study to develop validated human standards for repeat low level blast exposure based on current training DoD exposure guidelines. The goals of this effort are to further characterize the physiological response to blast exposure, to develop an algorithm that can be used in the development of an occupational standard for repeated blast exposures, to utilize survey and clinical assessment tools to understand the relationship of blast exposure and adverse outcomes, and to improve standards for acute exposure to blast overpressure events.

As part of this work, the investigators explored the impact of blast on breachers, specialists who obtain access to structures using explosives. In one study, 20 experienced breachers and 14 military non-breacher personnel underwent neuropsychological testing to assess cognitive and neurological function. Self-reported symptoms were also examined. The study revealed that experienced breachers reported ringing in the ears more than non-breachers. However, breachers performed better on several cognitive tests. The breachers also reported having more problems associated with memory, concentration, and irritability.

In a separate study, blood samples were collected daily from 97 Service members across three training sites for explosive breaching for two weeks. Self-reported TBI and blast exposure history was also documented. The blood was analyzed for levels of neurotrauma biomarkers (Aβ40, Aβ42, and tau). The study showed that those with a history of TBI had higher tau levels than other breachers before exposure to the blasts. Following a relatively larger blast at one of the training sites, the biomarker levels of those involved in the blast changed significantly, particularly for those with a history of TBI. These initial findings show that gene activity and the levels of their correlated proteins change after cumulative blast exposure. These results could impact current DoD blast exposure prevention and clinical practices since different mitigation strategies and/or treatments may be needed for blast exposure alone versus blunt force trauma if there are unique patterns resulting from blast exposure compared to blunt force trauma.

This effort was supported by DHA/JPC-5.

Effects of Repeated Blast Exposure on Markers of Neurodegeneration

Exposure to low levels of blast overpressure (BOP) may cause mild traumatic brain injury (mTBI) with progressive vascular and cellular changes that may contribute to neurodegeneration. To better understand this relationship, researchers at the Walter Reed Army Institute of Research (WRAIR; Silver Spring, MD) are studying two markers of neurodegeneration after repeated exposure to BOP: TDP-43, a very tightly regulated protein that is altered in neurodegenerative diseases such as frontotemporal lobar degeneration, and piezo2, a mechanosensitive ion channel previously shown to be dysregulated following blast exposure.

Using an advanced blast simulator that closely mimics "free-field" blast, rats were exposed one to four times to 13, 16, or 19 psi overpressure (n=6/group). TDP-43 levels were differentially affected by the number and magnitude of blast exposures, with the mean level being 38 percent greater in rats exposed multiple blasts of 16 psi compared to shams, and around 32 percent

Photo credit (opposite page): Spc. Nevada Jack Smith/DVIDSHUB

lower in rats exposed to only two blasts of varying intensities. Piezo2 levels were significantly higher in rats exposed to 19 psi blast compared with non-blasted shams (~17 percent), while levels were significantly decreased in rats exposed to 13 and 16 psi blasts (~52 percent), indicating that higher-intensity blast may have a differential effect on the brain's response to mechanical stimuli compared to lower-intensity blast. These findings suggest that cumulative effects of repeated exposures to blast may lead to pathophysiological changes in the brain, demonstrating a possible link between blast injury and neurodegenerative disease.

This effort was supported by USAMRMC.

Mechanics of Head Injury

Head Surrogates for Assessing Blast Overpressure Exposures

Blast exposures during training are controlled and maintained within safety standards, but there is concern over the effects of repeated exposure, even to low level overpressure. Quantifying the overpressure of a blast event in air is relatively straight forward, the challenge is to determine the amount of energy that penetrates into the brain. To this end, researchers at the U.S. Naval Research Laboratory (NRL; Washington, DC) and the Walter Reed Army Institute of Research (WRAIR; Silver Spring, MD) updated the NRL GelMan head into a modular format and constructed several gel-based brain surrogates with internal pressure sensors and accelerometers for mounting within the surrogate head.

A series of experiments examined overpressure penetration into the brain with and without a helmet in breacher training environments. Preliminary results from these studies indicate that at the highest overpressure exposure tested (approximately 100 kPa), the under-helmet pressure was approximately 40 percent of that measured at the eye. At low to moderate overpressures, the presence of a helmet resulted in an approximately 30 to 40 percent higher brain pressure than having no helmet. At the highest overpressure tested, pressure in the brain was approximately 70 percent higher in the helmet scenario than in the no-helmet scenario.

The improved NRL GelMan surrogates will enable greater understanding of the relationship between external overpressure and that experienced by the brain. This knowledge may be used to evaluate training practices (*e.g.*, change breaching stand-off distances) and develop better protective equipment.

This effort was managed by CDMRP with support and program oversight by MOMRP/JPC-5.

Structural Influence on the Mechanical Response of Swine Cranial Bone

In general, TBI studies that use impact and blast loading are conducted on animals rather than humans. However, the applicability of insight gained from non-human TBI impact and blast experiments relies on the ability to scale the animal injury thresholds to the human anatomy. The scaling relationship will depend on the mechanical response of the constituents of the human and animal head. The skull is particularly important since its mechanical response determines the transfer of deformation and stress to the brain during blast and impact loading.

The mechanical response of the skull, in turn, is dependent on its unique microstructure. Therefore, quantification of both the mechanical response and morphology of the animal skull will enable any critical injury thresholds identified in an animal TBI study to be scaled to other species, including human.

Ongoing investigations at the U.S. Army Research Laboratory (ARL; Aberdeen Proving Ground, MD) use the Göttingen minipig as a surrogate to better understand the mechanisms of TBI during mechanical loading. In FY18, the microstructure of cranial bone from adolescent (approximately six

months old) Göttingen minipigs was quantified and related to the mechanical response.

Bone specimens were dissected from the crania of adolescent Göttingen minipigs. The microstructure of these skull specimens was quantified using micro-computed tomography (microCT). The skull microstructure demonstrated a clear porosity dependence on location along the skull thickness; the skull was highly porous near the skin side surface and became less porous as the location approached the brain side surface. The skull specimens were then slowly compressed to measure their mechanical response. The distribution of strain on the specimen surfaces was measured to derive the stress-strain response and depth-dependent elasticity at different layers of the bone. These mechanical properties were then linked to structural properties using high-resolution images to produce a model. The model enabled the prediction of local elasticity and also provided an estimation of the tissue elasticity of the cranial bone. This work provides an understanding of the effect of force on the head for development of novel head protection devices to mitigate blast and impact loading to the head of the warfighter.

This effort was supported by ARL Applied Research Program.

Transparent, Tunable Polymer Models for Experimental Modeling of Blast-induced Brain Injury

Variation in neurological tissue properties due to age, gender, and species limit the usefulness of animal and cadaver studies in understanding the mechanisms of primary blast-induced traumatic brain injuries (bTBI). Biofidelic materials that simulate cranial tissues are needed to produce readily reproducible models for blast studies. Transparent materials could also enable high speed optical measurements during a blast experiment. Using such tissue simulants, it may be possible to compare post-blast results with post-mortem diagnostics of observed injuries in military Service members that sustained bTBI from an improvised explosive device. Researchers at the San Antonio Military Medical Center Department of Neurology (San Antonio, TX), the New Mexico Tech Department of Chemical Engineering (Socorro, NM), and Michigan State University Department of Mechanical Engineering (East Lansing, MI) have developed such materials, by exploring the use of transparent tunable polymers as cranial tissue simulants for bTBI experiments. These materials match physical properties of mammalian tissue and are transparent for high speed optical imaging during blast. They are either physically (natural gelatins) or chemically (polyacrylamide) gelled with the adjacent material to provide a more realistic cohesive material model. Of particular interest are separate material formulations to represent white, grey, and vascular tissue and a molding technique which provides a non-slip boundary between these materials. Mechanisms that are identified from these studies may ultimately be used to inform the design of protective gear to mitigate blast injuries.

Several natural and synthetic transparent gelatins were mechanically tested to find optimal formulations to represent white matter, grey matter, and vasculature. Bovine skin derived gelatin, bovine bone derived gelatin, and polyacrylamide gelatins, at varying weight-to-volume ratios, were used to achieve density values reported for human grey and white matter. The gels were tested for physical properties, including: elastic modulus, a measure of how much the material stretches in response to a force; fracture strength, a measure of how much force per unit area will tear the material; and shear modulus, a measure of how a material deforms when pulled different directions.

Choosing the ideal mix to represent tissue is complicated because material property data for human tissue in the literature are sparse and vary widely in terms of the methods and measurements achieved; however, there are broadly accepted values and good agreement on some relative parameters, such as that white matter is 20–30

percent stiffer than grey matter. Uniaxial tensile and compressive elastic moduli and shear modulus for brain tissue have been reported as roughly 5 kPa in tension, 14 kPa in compression, and 0.4–1.9 kPa in shear at comparable strain rates to these studies. Those values were well matched by polyacrylamide gels, at low strain rates, although at high strain rates the shear modulus is larger. Natural gelatins, on the other hand, had too large elastic and shear moduli at the weight to volume ratios tested.

Having selected formulations, the group made simulated brains for testing. Formulations that matched tissue properties were used to fabricate 30 cranial objects that were tested in a blast tube at two peak pressures and in two orientations (head-on, side-on blast). The materials were cast into 3D-printed molds in successive steps forming a test object with geometry representing the gross structure of the brain: the central sulcus, simplified gyri, sulci, ventricles, and vasculature. In each object, either natural or synthetic materials were used in conjunction to provide coupled material boundaries, such that adjacent grey and white matter material mimics adhered. Larger fluid vessels of about 4–5 mm were fabricated with polyacrylamide using a higher weight to volume ratio to represent vascular tissue. Smaller fluid filled vessels were made by leaving an empty cylinder when casting the gelatin, to represent smaller vessels of about one to three mm. The entire object was submerged in a cerebrospinal fluid mimic composed of normal saline and albumin (35 mg/dL) and enclosed by a 3D-printed case, with a simplified skull geometry and acrylic side windows for illumination and imaging. Care was taken to ensure that ventricles and vessels were fully perfused with fluid, with no bubbles in the sealed skull mimic before subjecting it to blast testing. Material boundaries and particles are readily observed through the model, allowing visualization of material motion and calculation of displacement at high temporal resolution. In a subset of fabricated cranial test objects, cavitation nuclei (microbubbles or phase-change nanodroplets) were embedded into gelatins to lower the energy threshold required for cavitation, making it possible to observe potential cavitation events and the resulting damage (Figure 7-2).

Three rounds of blast testing, each with ten test models, were carried out. The first round used gelatins derived from bovine skin and bone to model white and grey matter; the second round used polyacrylamide gels of varying density for grey and white matter and for large blood

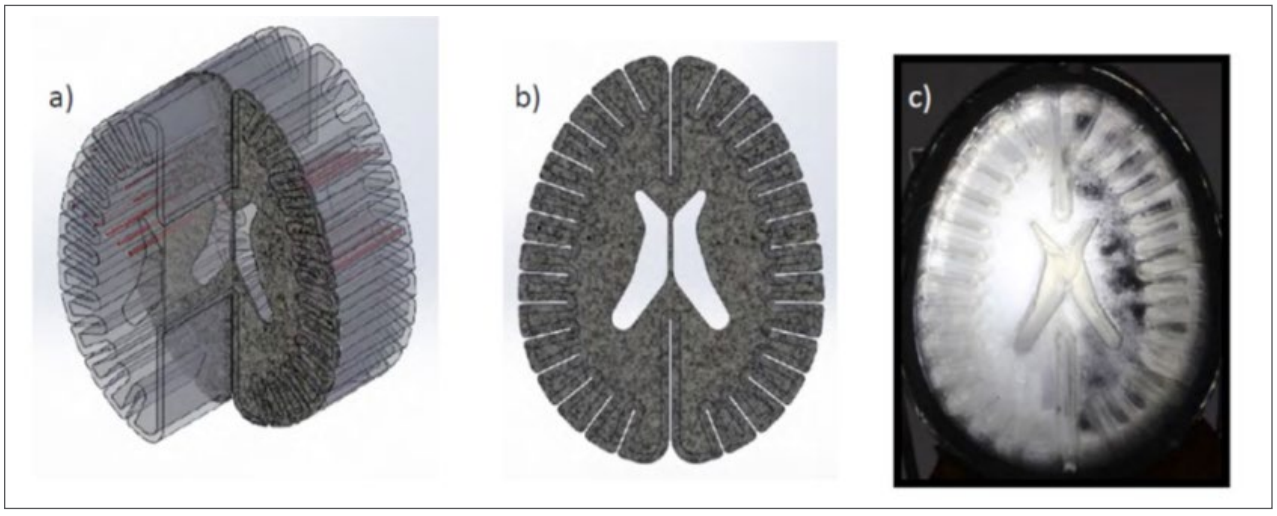


FIGURE 7-2: Figure tracks material deformation, showing transverse layers of particles deposited in the brain phantom. A) shows the intermediate layer in the midplane of the phantom; B) is a representation of how the particle plane would be seen through the transparent material of the phantom when using back illumination; and figure C) shows an axial view of a real phantom using back illumination. (Figure used with permission from the authors).

vessels. The third round used a different set of polyacrylamide densities to further match the material properties observed from biological measurements. In all tests, optical imaging data were collected for calculation of displacement and strain, pressure transducers were placed to monitor blast pressure, and photographs of the model before and after the blast were compared and analyzed.

All the test objects remained intact after blast exposure. No gross structural damage was observed; this result is consistent with medical imaging results of Soldiers exposed to improvised explosive device (IED) blasts. At high blast pressures (around 75 psi), gas coalescence was observed in the periventricular region of two objects containing cavitation nuclei, suggesting that the fluid-gel boundary may be more susceptible to injury. Early results show maximization of model tissue deformation at the brain surface and gray matter. These regions also are preferentially scarred in human subjects after blast injury and such a finding may provide insight into possible mechanisms of this scarring pattern.

This project is the first to fabricate blast test objects using natural and synthetic gelatin materials in an effort to capture the material property differences at various tissue boundaries composed of grey/white matter, vascular tissue, and cerebrospinal fluid. The data collected can inform the validation of simulations in which a blast wave interacts with tissue. A limitation of the approach is imperfect matching of the total strain and maximum strain rates observed with typical materials characterization techniques between human tissue and mimetic materials. Characterization of microbubble and phase-change nanodroplets properties in these materials is underway to develop a diagnostic for the forces experienced by the material during blast. This project is ongoing, and this knowledge will be harnessed to modify current combat helmets with the goal of reducing brain deformation during blast and perhaps providing improved protection for Service members.

This effort was supported by the Air Force Medical Service and is strategically aligned with 2015 ICL (RTK) AFMS 29, AMC A1, A3, E3, JPC-6.

Equipment Testing

Blast Induced Injuries to the Dismounted Soldier

Recent conflicts have highlighted the threat posed to dismounted Soldiers by buried explosives that result in severe soft tissue damage to the extremities and urogenital areas. Many areas of the body injured during buried blast events are not protected by body armor and are only covered by the combat uniform. Researchers at the Army Research Laboratory (ARL; Aberdeen Proving Ground, MD) have performed experiments and simulations to reduce vulnerability of the dismounted Soldier.

Buried explosive arena experiments were performed to characterize the secondary debris component of buried blast events so that the loading can be replicated through more controlled, nonexplosive, and less expensive methods (*Spink, 2018*). Specially designed shields, placed at the perimeter of the arena (1m from the exploding source), allowed some debris to pass through where it could be recorded by high speed video. Roadbed and cross-country compaction specifications were evaluated and used to establish the speed and angle of the debris. Fabric targets backed by half-cylinders made of silicon rubber were placed at the same 1m distance to evaluate the resulting damage to the fabric from the buried blast.

The goal of this simulation was to identify aspects of fabric design that contribute to performance in order to optimize the fabric for protection from buried blast events. The simulations illustrated how impact direction, fiber material, and yarn construction influenced the amount of tearing and skin exposure. The results showed that deflection patterns and fabric texture resulted in higher stress and failure during oblique impact compared to a

normal impact to the extremities and urogenital areas. The use of continuous filament yarns or 100 percent aramid ripstop yarns reduced fabric tearing and exposure compared to the staple yarns currently used in the uniform fabric. These findings demonstrate the impact of uniform fabric on injury resulting from explosion and provide a viable option to reduce extremity and urogenital injuries in the field.

This effort was supported by ARL Applied Research Program.

The Impact of Armor Strength on Lung Injury In Open-field Blasts

Researchers at U.S. Army Institute of Surgical Research (USAISR; Fort Sam Houston, Texas) in collaboration with the Institute de Recherche Biomedical des Armees (IRBA; France) investigated the impact of open-field blast exposure on lung injury and the protection provided by armor of different strength using a pig blast model. Anesthetized swine with soft body armor, hard body armor, or no armor were subjected to open-field blast exposure. Blood samples were collected at baseline, 30 minutes, and 60 minutes after blast exposure. Lungs were collected 60 minutes post blast exposure for analysis.

After exposure to open-field blast, lung tissue from swine either without protection or with soft body armor had significant vessel swelling and hemorrhaging. Interestingly, lung tissue from pigs not exposed to blast and those exposed to blast and protected by hard body armor exhibited normal tissue structure. In all animals exposed to open-field blast, proinflammatory proteins interleukin (IL)-1beta and IL-18 were detected at significantly higher levels in the blood in comparison to animals not exposed to blast; this suggests that isolated open-field blast exposure induces an acute and distinct expression profile of inflammatory proteins. Proinflammatory proteins TGF-beta 1 and TGF-beta 2 were higher in the plasma of both unprotected animals and animals with soft body armor exposed to blast. However, animals with hard armor protection did not have increased levels of TGF-beta 1 and TGF-beta 2 in plasma, implying that hard body armor protection not only prevents pulmonary injury, but also attenuates the acute release of inflammatory proteins due to tissue damage caused by blast exposure.

These findings show that armor strength impacts the extent of lung injury following open-field blast exposure in part through attenuation of the inflammatory response, providing support for the importance of resilient armor against blast injury.

This effort was supported by CCCRP/JPC-6.

Joint Light Tactical Vehicle Blast Injury Mitigation

In FY18, the Joint Program Office (JPO) for Joint Light Tactical Vehicles (JLTV) performed platform interoperability testing. The purpose of this testing was to certify that the on-board Blue Force Tracker and the Tactical Ground Reporting System will enable near real-time situational awareness as part of the Common Operating Picture during mission operations.

This capability will serve to enable mitigation of blast injuries both by threat avoidance and by rapid actionable response to enemy operations. JPO JLTV also received the Final Low Rate Initial Production Full Up System Level Live Fire Test Report generated by the Aberdeen Test Center. Analysis of this report and supporting data will continue to identify areas of future potential improvement to the current JLTV detailed design against a dynamic and evolving threat environment (Figure 7-3).

This effort was supported by PEO CS&CSS, and the JPO JLTV.

FIGURE 7-3: Joint Light Tactical Vehicles. (Figure used with permission from the authors).

Forensic Outcomes of Vehicle-borne Improvised Explosive Devices

Researchers at the U.S. Army Engineer Research and Development Center (ERDC; Vicksburg, MS) in partnership with the National Ground Intelligence Center (NGIC; Charlottesville, VA), the United States Army Tank Automotive Research, Development and Engineering Center (TARDEC; Warren, MI) and the U.S. Army Research Laboratory (ARL; Aberdeen Proving Ground, MD) are conducting a series of studies with the goal of developing technologies, procedures, and training to enable identification of weapons systems, involved in attacks on U.S. and Allied Forces using forensic data collected at post-attack scenes. In a key study, ERDC researchers are evaluating the forensic outcome of vehicle-borne improvised explosive devices (VBIEDs) using convoy VBIED experiments that simulate attacks against military vehicles. Occupancy injury related to VBIED blast events are captured using onboard instrumentation.

Hazards from VBIED events are quantified and correlated to observed forensic data, and damage to vehicles and structures. Overall, these efforts provide critical insight into blast effects from these types of threats on vehicle occupants and may be used for improvements in protective design systems.

This effort was supported by NGIC.

Computational Modeling and Simulations

Computational Modeling of Blast Wave Transmission Through Human Ear

Understanding how blast waves propagate through the human ear is a necessary step in the development of effective hearing protection devices. Researchers from the University of Oklahoma (Norman, OK) have constructed the first 3D finite element (FE) model to simulate blast wave transmission through the ear and validated it with measurements from cadaver studies (*Leckness, Nakmali, and Gan, 2018*).

Pressures measured at the ear canal of cadaver temporal bone specimens exposed to blast

overpressure from vertical, horizontal, and frontal directions were applied at the entrance of the ear canal in the model and ranged from 50 to 80 kPa. The pressure waveforms near the tympanic membrane (TM) in the canal (P1) and behind the TM in the middle ear cavity (P2) were calculated. The model-predicted results were then compared with measured P1 and P2 waveforms recorded in human cadaver ears during blast tests. For the P1 location, the error in the model-predicted peak pressure level was 3.0, 25, and 20 percent, for the vertical, horizontal, and front blast directions, respectively. Error for A-duration was 9.1, 17, and 13 percent for the vertical, horizontal, and front blast directions, respectively. Finally, the error in the model-predicted 1ms kurtosis was 15, one, and 9.8 percent for the vertical, horizontal, and front blast directions, respectively. Qualitative assessment of P2 wave forms indicated good agreement between model and cadaver results. The FE model will be used to improve auditory hazard assessment models and better understand blast wave transmission through the human ear. Ultimately, these efforts will contribute to the development of advanced hearing protection devices.

This effort was managed by CDMRP with support from PH/TBIRP and MOMRP/JPC-5.

Computation Fluid Dynamics Model of Blast Eye Injury

The Warfighter Performance Group at the U.S. Army Aeromedical Research Lab (Fort Rucker, AL) developed a computational fluid dynamics model to investigate the response of ocular tissue to blast overpressure. Unlike related blast simulations that incorporate a detonation model to propagate a blast wave through the eye and orbit, this model applied a pressure directly to the corneal surface, eliminating the need to model the complex interaction of the blast wave with eye protection and the orbit. A human eye model was integrated into ANSYS AUTODYN using an explicit solver. Material properties for the cornea, sclera, choroid, retina, aqueous, and lens were defined. A Eulerian reference frame was used for the aqueous and lens while the rest of the tissue was assigned a Lagrangian reference frame. A patch independent tetrahedral mesh was then developed for the eye model. A distributed pressure was applied to the cornea and the front of the sclera and was allowed to behave as a Friedlander waveform.

Nine scenarios were analyzed for peak pressures between 0.207 and 1.03 MPa. Maximum displacements and stresses were shown to have a linear relationship with the applied pressure. The highest stresses were recorded on the sclera, and the highest displacements were recorded on the corneoscleral shell. Large displacement measurements for the retina were seen with greater than 0.621 MPa reflected pressures, which may indicate retinal tear or detachment. Results from this model are largely comparable to data from other simulations that employed a detonation model. Some differences were noted due to the absence of a bony orbit in this model, which manifested by faster decay times in tissue stress due to reductions in reflective pressures from the orbit. Overall these results (presented at the 2018 Military Health System Research Symposium) suggest that ocular tissue is susceptible to primary blast injury. Protective eyewear may be integrated into the model to evaluate the protection provided by different eyewear designs.

This effort was supported by USAMRMC.

Bioenergetics of Amputee Gait

Decades of research indicates that a below-knee amputation negatively affects walking mechanics and the metabolic cost of walking. Researchers with the Extremity Trauma and Amputation Center of Excellence at Brooke Army Medical Center (BAMC; Fort Sam Houston, TX), in partnership with collaborators at the University of Maryland (College Park, MD), hypothesized that maintaining muscle strength after limb loss

may mitigate the high metabolic cost of walking typically seen in the larger general limb loss population.

The research team used musculoskeletal modeling and optimal control simulations to perform a longitudinal study (25 virtual "subjects") of the metabolic cost of walking pre- and post-below-knee limb loss (*Esposito and Miller, 2018*). Simulations of walking were first performed pre-limb loss on a model with two intact biological legs, then post-limb loss on a model with a passive prosthetic foot. Metabolic costs were compared pre- vs. post-limb loss, with systematic modifications to the muscle strength and prosthesis type (passive, powered) in the post-limb loss model. The metobolic cost in models with a passive prosthesis did not increase above the pre-limb loss cost if pre-limb loss muscle strength was maintained, particularly in the residual limb. A powered prosthesis compensated for up to 20 percent loss of strength.

The present simulation results support recent experimental data suggesting an increase in the metabolic cost of walking is not an inevitable consequence of unilateral below-knee limb loss: an increase in metabolic cost may be driven more by loss of strength in the remaining muscles rather than loss of the limb.

This effort was supported by AMEDD Advanced Medical Technologies Initiative (AAMTI), Military Amputee Research Program (MARP), and Center for Rehabilitation Sciences Research (CRSR).

Oxidative Stress and Antioxidant Treatment

Characterization of Blast Injury in an Animal Model to Support Development of a Human Blast Injury Criterion

There is a large body of work examining blast exposures and blunt impact on brain injury in animal models, but their correlations to the human condition are less well defined. Researchers at the New Jersey Institute of Technology (NJIT; Newark, NJ) are working toward a validated master dose-response curve for blast exposure that correlates the biomechanical properties of blast waves to specific brain tissue injuries in a manner that is independent of blunt injury. This goal furthers their long-term objective to produce an interspecies transfer function and develop a human "Blast Injury Criterion" for assessing the risk of brain injury in humans exposed to a single or repeated blast.

A number of findings towards this aim have recently been published. In rats exposed to a single 180 kPa overpressure event in a shock tube, levels of NOX 1 and NOX 2 (nicotinamide adenine dinucleotide phosphate oxidase 1 and 2), a superoxide producing enzyme, in the cerebellum and cerebral hemisphere were significantly higher than in sham controls four hours after exposure (*Rama Rao et al., 2018*). Correspondingly, levels of superoxide were significantly higher in the frontal cortex, hippocampus, thalamus, and cerebellum of blast-exposed animals than in sham controls. These observations indicate that there is an increase in oxidative stress and oxidative damage occurring in the brain in the acute phase of blast exposure.

In a separate study of a single blast event, rats exposed to 180 kPa overpressure experienced disruption of the blood-brain barrier as measured by the concentration of tracer agents (*e.g.*, Evans blue dye and sodium fluorescein) peaking in the brain parenchyma four hours after injury and returning to pre-injury levels within 24 hours (*Kuriakose, et al., 2018*). The most robust changes occurred in the frontal cortex, striatum, and thalamus, while minimal to no statistically significant extravasation was observed in the cerebellum, demonstrating an anterior to posterior pattern of differential blood-brain barrier permeability. In addition, separate studies on rats exposed to a single 110-130 kPa

overpressure event suggest that the highest intensity of electrophysiological activity occurred in cerebellum within the first 24 hours after injury (*Ordek et al., 2018*).

Ultimately, this work supports the development of dose-response curves correlating blast exposure levels to specific types of pathological findings. This knowledge will inform the design of improved diagnostics and personal protective equipment for Service members.

This effort was managed by CDMRP with support from PH/TBIRP and MOMRP/JPC-5.

A Diet High in Antioxidants or Ketones and Omega-3 Preserve Vision and Optic Nerve Axon Structure

Researchers from Vanderbilt University (Nashville, TN) conducted a study to investigate the role of oxidative stress and inflammation in optic nerve degeneration and vision impairment resulting from traumatic events. The study design entailed exposing mice to repeated eye-directed over-pressure air blasts. Levels of antioxidants in the retina were manipulated by feeding the animals diets high in antioxidants (vitamin C and vitamin E) or a highly ketogenic diet for weeks prior to and following injury. Assessment of the animals on regular diet two and four weeks after injury revealed increased levels of free radical superoxide, activated the interleukin-1 (IL-1) inflammatory pathway proteins; extensive axon degeneration, and substantial vision loss. Mice fed the high antioxidant diet had higher tissue levels of vitamin E and lower superoxide, and the IL-1 pathway was not activated. Animals on the antioxidant diets also exhibited less axon degeneration (Figure 7-4) and preservation of vision.

Animals specifically on the ketogenic diet had higher serum ketone levels and lower tissue levels of superoxide compared to those on a ketogenic control diet. The ketogenic diet also blocked activation of the IL-1 pathway. The ketogenic diet was also found to preserve vision and prevent axon degeneration after injury.

Taken together, these findings suggest that a high antioxidant diet may be neuroprotective and lead to improved visual outcomes after neurotrauma.

This effort was managed by CDMRP with support from PH/TBIRP and programmatic oversight by CRMRP/JPC-8.

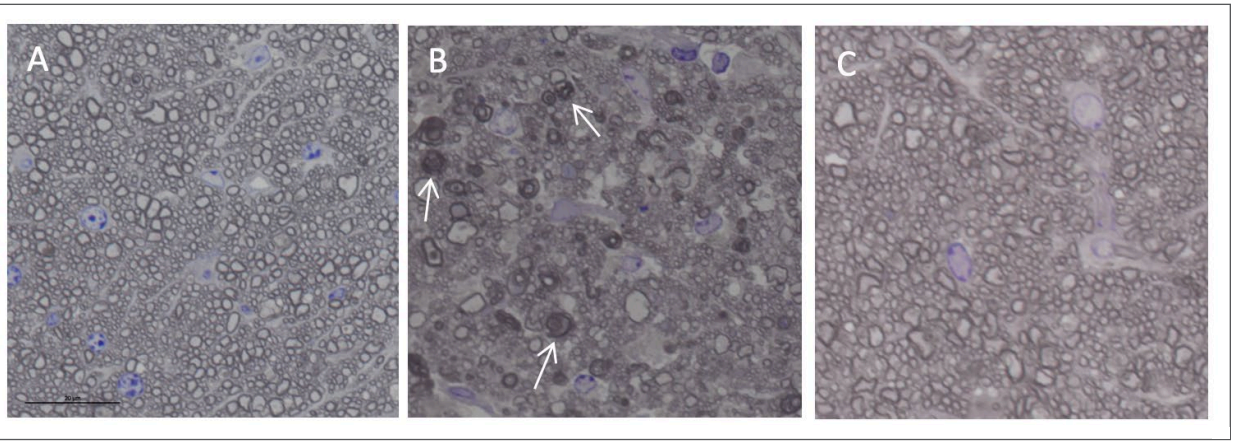


FIGURE 7-4: High-resolution images of optic nerve cross-sections. A) Sham, B) 2-weeks post-injury on regular diet, C) 2-weeks post-injury on high vitamin C and vitamin E diet. Blue – cells, gray – myelin sheath around axons. Arrows indicated degenerative profiles. (Figure used with permission from the authors).

Photo credit: Courtesy Photo/U.S. Army

Impact of Dietary Omega-3 Fatty Acid Deficiency on Blast TBI and Traumatic Stress

U.S. Soldiers suffer a high incidence of traumatic brain injuries from exposure to explosions (blast TBI). There is also a high co-morbidity of blast TBI and subsequent post traumatic stress disorder (PTSD). Nutritional countermeasures could be a safe, readily translatable approach to preventing these debilitations. Long chain omega-3 polyunsaturated fatty acids ("omega-3s") may be an important component of such a countermeasure because omega-3s are crucial building blocks of neuronal membranes and attenuate inflammation processes. Dietary deficiency of omega-3s is a known risk factor for neurodegenerative and neuropsychiatric disorders.

Using rats as a model, researchers at the Walter Reed Army Institute of Research (WRAIR; Silver Spring, MD) explored the impact of an omega-3-poor diet on vulnerability to blast TBI and PTSD. Adult male rats were maintained for six weeks on diets devoid of omega-3s. To induce TBI, animals were then exposed to a blast overpressure wave in an advanced blast simulator, followed by a head-concussion caused by a dropped weight. A different group of rats was briefly subjected to immersion underwater to induce traumatic stress. Animals continued their special diet and were assessed out to two weeks post-insult. Neurobehavioral function was evaluated by studying the ability of the rats to maintain balance on a twirled rod, and by using an "elevated plus maze," a specially designed environment to assess the rats' preference for darkened, protected environments as a measure of anxiety. Neuropathological status of their brains was determined using silver staining to see the brain cell structures, and by genomic array screening to look for changes in genetic expression in the brain. The rats' plasma was assayed for stress hormone levels.

Results show that blast TBI leads to neurobehavioral impairments, accompanied by

neuronal cell degeneration, and related changes in brain gene expression. Traumatic stress produced aberrant behaviors and neuroendocrine imbalances. Impact of the omega-3 deficient diet is greater on traumatic stress than on blast TBI, an observation that is consistent with omega-3s playing a major role in stabilizing behavior-altering neurotransmitters. Future directions will address the consequences of omega-3 deprivation when the two insults are combined.

This effort was supported by MOMRP/JPC-5.

Extremity Injuries

Major Deployment-Related Amputations in the U.S. Armed Forces, 2001–2017

Loss of limb from combat injuries can have dramatic effects on the quality of life of Service members and their families. Understanding the scope of these injuries is necessary for planning and maintaining appropriate support services in the DoD and Department of Veterans Affairs (VA). Researchers at the DoD/VA Extremity Trauma and Amputation Center of Excellence (EACE) surveilled the Expeditionary Medical Encounter Database to collect data on the numbers, types, and anatomic locations of deployment-related major lower and upper limb amputations, and the demographics and military characteristics of this cohort from 2001 through 2017 (*Farrokhi et al., 2018*).

Over this time period, 1,705 Service members had deployment-related major amputations. This group includes those with bilateral lower limb (n = 418) and upper limb amputation (n = 18), triple amputees (n = 46), and quadruple amputees (n = 6). The majority of lower limb amputations were transtibial (n = 995; 52 percent). Transradial amputations (n = 114; 38 percent) composed the largest category for upper limb loss. The amputees were mostly male (98 percent), primarily non-Hispanic white (76 percent), 21–29 years old at the time of injury (66 percent) and served in the Army or Marine Corps (67 and 29 percent, respectively). Trends in the incidence of injuries leading to limb loss followed patterns of the scope and intensity of ground combat operations. These data are critical for formulating sound, current and future policy, healthcare, and readiness decisions.

This effort was supported by EACE.

Program Area: Acute Treatment

Research in acute treatment is intended to improve survivability and mitigate long-term disability for Service members with the full spectrum of injuries following blast events. Collaborations between DoD and partners in the FDA, academia, and the private sector are investigating new diagnostic tools, therapies for TBI, hemorrhage control devices, strategies to mitigate wound infection, and interventions for facial, auditory, and visual injuries. This section demonstrates how the research community is employing novel neuroimaging techniques, evaluating clinical data, and experimenting in the laboratory to address the spectrum of blast injuries. The combined research efforts will improve (1) our understanding of the capabilities and limitations of current technologies; (2) design of new tools; (3) methods to validate injury mitigation in the prehospital setting; and (4) diagnostics and clinical guidelines for the acute treatment of blast injuries.

Hemorrhage Control and Resuscitation

Conventional Endovascular Acute Hemorrhage Control by Common Balloon Occlusion Methodologies May be Inaccurate and Should Account for Age and Anatomic Location

Endovascular balloon occlusion is used to control non-compressible hemorrhage. Recently an imaging-free endovascular navigation technique, which uses specific body landmarks to predict

the correct arterial location for insertion, has become increasingly popular because of its potential to reduce imaging requirements for endovascular acute hemorrhage control. However, due to variation in body curvature this mapping could potentially lead to inaccurate placement. Additionally, optimal parameters for balloon occlusion pressures and volumes to control bleeding without causing artery injury are not clearly defined.

Researchers at the University of Nebraska Medical Center (Omaha, NE) address these issues in a study to accurately quantify and analyze the layout of arteries in the torso of trauma populations to validate the utility of the arterial "roadmaps" used in this recently developed navigation technique to determine burst pressure ranges in the most common balloon occlusion locations for endovascular hemorrhage control in the abdominal and thoracic aorta.

The study analyzed CT angiograms (CTAs) from 86 trauma patients to build a 3D-computer model of the aorta and branching arteries. Conventional suprasternal notch lengths taking belly curvature into consideration were determined. The results suggest conventional suprasternal notch lengths may substantially overestimate endovascular device insertion distances with increasing belly curvature, which may result in misplacement of devices into the aortic arch branches or into the heart. Use of xiphoid process distances can substantially reduce the frequency of misplacements in all body sizes; however, even when the precise length of the catheter is known, misplacements can still occur in older subjects with tortuous anatomy.

To define optimal occlusion pressures, aortic occlusion was performed in various locations within 53 donor aortas under flow pressure. The study revealed that safe balloon occlusion pressures and volumes depend on age and anatomic location.

Accurate characterization of vascular location, distribution, and burst pressure ranges could drastically improve survival of vascular trauma victims and inform the development of next generation endovascular hemorrhage control devices to improve safety and use.

This effort was managed by CDMRP with support and program oversight by CCCRP/JPC-6.

Treatment Using Soluble Drag Reducing Polymers in Resuscitation Fluid Following Traumatic Brain Injury with Concomitant Hemorrhagic Shock

A serious complicating factor in traumatic brain injury (TBI) is low arterial blood pressure due to hemorrhagic shock caused by extremity of injuries and/or shrapnel after explosion. Current immediate treatments for TBI with concomitant hemorrhagic shock (TBI/HS) are based on volume restoration to raise arterial pressure by resuscitation fluids (RF). While these fluids may be effective in restoring arterial pressure and improving blood circulation in large vessels, they do not target impaired circulation within small vessels (capillaries) in the brain, leading to neuronal death. Small quantities of blood soluble, drag reducing polymers (DRP) can improve oxygen supply to the brain by enhancing blood flow in capillaries, thus reducing death of neurons near sites of injury following TBI/HS.

To test this theory, investigators at the University of New Mexico Health Sciences Center (Albuquerque, NM) and University of Pittsburgh (Pittsburgh, PA) evaluated the acute and prolonged beneficial effects of adding nanomolar quantities of blood soluble DRPs to the resuscitation fluid (DRP-RF) for up to six hours after TBI/HS in rats. The animals sustained a TBI followed by controlled HS. The rats were infused with DRP-RF or RF followed by blood reinfusion. It was determined that modulation of blood flow using DRP-RF effectively restores cerebral microcirculation and protects neurons after TBI complicated by hemorrhagic shock by

preventing blood clot formation in capillaries in the brain and thus, reducing hypoxia. In addition, DRP-RF requires infusion of a lower volume to improve tissue perfusion and oxygen utilization, which reduces brain swelling due to excess fluid in the blood, which often occurs with a standard fluid resuscitation.

In summary, immediate treatment with DRP-RF improves neurological outcomes and may reduce mortality and post-traumatic neurological disabilities.

This effort was managed by CDMRP with support from PH/TBIRP and programmatic oversight by CCCRP/JPC-6.

SynthoPlate, a Synthetic Platelet Substitute, Reduces Blood Loss, Stabilizes Blood Pressure, and Significantly Improves Survival Following Multiple Types of Traumatic Bleeding Injuries

Combat trauma-associated uncontrolled hemorrhage and coagulopathy remain the leading causes of morbidity and mortality in the military. Overwhelming evidence from military-based resuscitation studies has indicated that platelet transfusion can significantly reduce these events in prolonged field care scenarios. However, platelet transfusion suffers from unique logistical and functional challenges in a military setting due to the limited availability and portability of platelet concentrates, special storage requirements, high risk of bacterial contamination, and very short shelf-life of plasma products. Furthermore, blood type compatibility issues can limit early in-field and en route intervention.

These challenges have led to robust research efforts for creating a shelf-stable, highly portable, readily deliverable 'platelet surrogate' that can mimic platelet-mediated mechanisms of hemostasis, while avoiding a systemic immune response and unexpected harmful effects. To this end, researchers at Case Western Reserve University (Cleveland, OH), the University of Pittsburgh (Pittsburgh, PA) with the United States Army Institute for Surgical Research (USAISR; San Antonio, TX) developed a lipid-peptide conjugate-based intravenously administrable synthetic platelet nanotechnology, called SynthoPlate, that mimics the platelet's hemostatic mechanisms specifically at the hemorrhaging sites for targeted activity (Figure 7-5).

In two recent studies, the team examined the effect of SynthoPlate in two animal models of hemorrhagic injury (*Dyer et al., 2018; Hickman et al., 2018*). In the first study, mice sustained a liver injury and were administered SynthoPlate intravenously as pretreatment or after injury via transfusion. Regardless of treatment order, SynthoPlate reduced blood loss and delayed development of hypertension.

The second study investigated the impact of intravenous SynthoPlate administration in a femoral artery hemorrhage model in pigs, during the first couple of hours after injury, a time when interventions can have a significant impact on

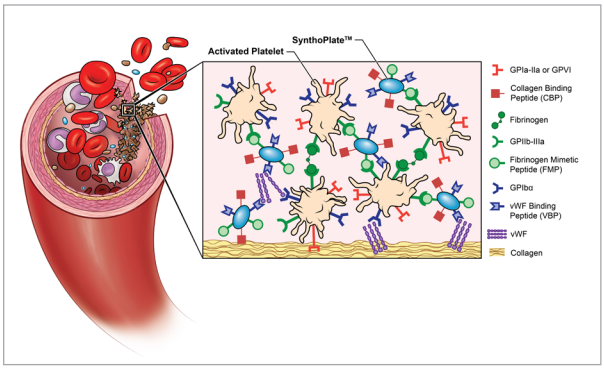


FIGURE 7-5: Illustration of the mechanism by which the synthetic platelet surrogate technology, SynthoPlate, augments hemostasis; SynthoPlate (blue particles) are nanoparticles decorated with a combination of protein components (peptides) that bind various blood proteins–vWF-binding peptides (VBP), collagen-binding peptides (CBP) and active platelet integrin GPIIb-IIIa binding fibrinogen-mimetic peptides (FMP); In the event of a hemorrhagic injury, SynthoPlate can target to the hemorrhaging site by binding to exposed vWF (a blood protein) and collagen (thus mimicking platelet's adhesion mechanism) and can aggregate with active platelets via binding to protein GPIIb-IIIa (thus mimicking platelet's aggregation mechanism); these mechanisms occurring in tandem accelerate hemostatic plug formation and improve hemorrhage control. (Figure used with permission from the authors).

patient outcome. Again, SynthoPlate treatment reduced blood loss, stabilized blood pressure, and significantly improved survival.

Taken together, these findings support the potential use of SynthoPlate as a viable platelet surrogate for emergency management of traumatic bleeding in military and civilian settings. Development of a platelet surrogate could greatly resolve military-relevant challenges regarding hemostatic management of traumatic hemorrhage by platelet-transfusion and significantly advance prolonged field care treatment modalities in combat wound care.

This effort was managed by CDMRP with support and program oversight by CCCRP/JPC-6.

Demonstration of Safety Analysis of Freeze-dried Plasma in Normal Healthy Volunteers

Current standard of care for hemorrhage on the battlefield involves infusion of blood components such as fresh frozen plasma (FFP) and liquid-stored platelets, which can only be stored and administered at reasonably equipped (Role of Care 3) facilities. Freeze-dried plasma (FDP) offers coagulation therapy and volume replacement for hemorrhaging patients in a logistically superior manner by virtue of its ability to be stored at ambient temperature and carried by medics into the field where it can be administered at the point of injury.

Vascular Solutions/Teleflex, the commercial manufacturer of FDP (Wayne, PA), recently completed a 24-subject Phase 1 clinical study. Three cohorts of eight healthy volunteers were infused with either one, two, or three units of autologous FDP. The cohort receiving three units of FDP also received three units of autologous FFP in a double-blinded crossover study design at a 14-day interval. All subjects were monitored at intervals up to 28 days and all were shown to tolerate the FDP infusion, with no serious adverse events and no significant treatment-related adverse events (*Cancelas et al., 2018*).

Vascular Solutions/Teleflex, under a cooperative research and development agreement (CRADA) with U.S. Army Medical Materiel Development Activity (USAMMDA; Fort Detrick, MD), has recently validated a second generation lyophilization (freeze drying) bag and accompanying manufacturing process for large-scale production.

Plasma is a vital treatment for hemorrhage. This study demonstrates the safety of FDP for use on the battlefield when plasma is not available.

This effort was supported by USAMMDA.

Emerging Technologies for Hemorrhage Control Using a Porcine Model of Combined Pelvic and Vascular Injury

Non-compressible truncal hemorrhage (NCTH) accounts for approximately 24 percent of potentially survivable battlefield hemorrhage mortality cases. One of the major contributors to NCTH is major pelvic fracture with concomitant pelvic vascular injury. Currently, there is no universally accepted means of controlling hemorrhage associated with pelvic vascular injuries and pelvic fractures. Several emerging technologies (*e.g.*, a laparoscopic balloon dissector and self-expanding foam) are showing promise as are recent evaluation of more traditional methods of hemorrhage control.

Researchers at Madigan Army Medical Center (Tacoma, WA) are conducting a study to develop a pig model of combined pelvic and vascular injury and then test the ability of these interventions to arrest pelvic bleeding and stabilize hemodynamics. The study was recently presented at several conferences discussing potential minimally invasive treatment options, such as preperitoneal balloon tamponades and an abdominal aortic junctional tourniquet for pelvic fracture-associated hemorrhage in disaster scenarios.

The use of a laparoscopic balloon dissector (*e.g.*, REBOA) and/or injectable self-expanding foam will

allow forward surgical units to better and more safely stabilize casualties with life-threatening pelvic hemorrhage.

This effort was managed by CDMRP with support and program oversight by CCCRP/JPC-6.

Neuromuscular Control and Balance

Vestibular/Ocular Motor Screening: A Reliable Tool to Evaluate Mild Traumatic Brain Injury in a Military Clinic Setting
Mild traumatic brain injury (mTBI) from blast often causes dizziness, vertigo, and imbalance resulting from the injured brain's inability to integrate head and eye movements. The Vestibular/Ocular Motor Screening (VOMS) is a five-minute clinical screening tool developed at the University of Pittsburgh (Pittsburgh, PA), to identify and track recovery in Service members with mTBI from blast and other causes. The VOMS requires very limited equipment (a small stick with a 14-point font target on it), complements current assessment tools used by military medical personnel, and can be administered in both combat and non-combat environments. To determine if the VOMS can distinguish healthy Service members from those with blast and other mTBI, and track recovery, researchers at the University of Pittsburgh trained military medical personnel to use the VOMS using a modified Balance Error Scoring System (mBESS) training video. To date, nearly 200 baseline and post-injury VOMS tests have been conducted, and preliminary reliability of the tool in Service members has been established (*Kontos et al., 2018*). The VOMS provides a pathway to better diagnosis, determination of recovery, and earlier and more effective treatment; thereby, reducing the financial, personal, and societal burden to Service members from blast-related mTBI.

This effort was managed by CDMRP with support from PH/TBIRP and programmatic oversight by CRMRP/JPC-8.

The Expanded Automatic Assessment of Postural Stability: The xAAPS
Researchers at Temple University (Philadelphia, PA) have created the Expanded Automatic Assessment of Postural Stability (xAAPS), a system that tracks personnel as they perform a series of movement assessments. The xAAPS then scores those movements in the same way that a trained human observer would. Because the xAAPS uses inexpensive off-the-shelf sensors and a custom Windows application, it can be deployed anywhere and operated by anyone.

Building on the first generation AAPS that evaluated static posture (*Glass et al., 2018*), the proof-of-concept xAAPS system implements three of the seven movements of the well-known Functional Movement Screen (FMS), and the core technology can be readily adapted for other movement screens or action as needed. The xAAPS is built around commodity markerless motion tracking devices such as the Microsoft Kinect v2.0 and other depth cameras such as the Orbbec Astra.

The researchers have performed a validation experiment with the xAAPS, comparing its scores to those from an experienced human observer for FMS deep squat, hurdle step, and in-line lunge movements from healthy adults ($n = 26$) (*Napoli et al., 2018*). The xAAPS performed better than random classification and produced accuracies of 92.3 percent for the deep squat, 84.6 percent for the hurdle step, and 69.2 percent for the in-line lunge. These results demonstrate that the xAAPS can be a valuable in-field expedient to evaluate dynamic balance without the need of human scorers.

This effort was managed by CDMRP with support from PH/TBIRP and programmatic oversight by CRMRP/JPC-8.

Validity and Reliability of Smartphone Orientation Measurement to Quantify Dynamic Balance Function

A collaboration led by researchers at the University of North Carolina (Greensboro, NC) has developed a novel smartphone-based neuromotor assessment protocol for screening of dynamic balance deficits stemming from head trauma. The reliability and validity of this Android app, called AccWalker, were evaluated in a recent publication (*Kuznetsov et al., 2018*).

The AccWalker orientation detection algorithms were compared to a biomechanics laboratory motion capture system using a pendulum (*i.e.*, non-biological movement) and a human stepping task (*i.e.*, biological movement). The test-retest reliability of a stepping-in-place protocol in three different sensory conditions (eyes open, no-vision, head shake) was also evaluated using temporal and spatial variability metrics extracted from thigh orientation signal in a sample of healthy young adults. Results suggest that smartphone sensors provided valid measurements of movement timing and amplitude variables but were sensitive to anatomical placement. In addition, the fidelity of measurements compared to the laboratory-system was dependent on the version of sensor firmware and Android OS running on the smartphone. High test-retest reliability was shown for the temporal and spatial variables of interest during the stepping-in-place task. The researchers plan to collect data from healthy Service members to develop a baseline dataset.

Collectively, these experiments suggest that the AccWalker smartphone application is a valid and reliable way to measure leg movement characteristics during dynamic balance activity, which could provide an objective way to assess neuromotor function after head trauma closer to the point-of-injury.

This effort was managed by CDMRP with support and program oversight by CRMRP/JPC-8.

Trunk Muscle Activation Patterns During Walking Among Persons with Lower Limb Loss

Persons with lower limb amputation (LLA) experience an increased incidence of low back pain (LBP). Researchers at the DoD/Department of Veterans Affairs (VA) Extremity Trauma and Amputation Center of Excellence (EACE) studied the underlying trunk muscle activation patterns associated with walking to provide insight into neuromuscular control strategies post LLA and help determine causes of LBP (*Butowicz et al., 2018*).

Participants with unilateral LLA (n = 8) and controls (n = 10) walked over ground at 1.0, 1.3, and 1.6 m/s, and at self-selected speeds. Trunk muscle onsets and offsets of were determined from electromyography activity of bilateral thoracic (TES) and lumbar erector spinae (LES). Trunk-pelvic kinematics were also recorded.

Initial TES onset times did not differ between groups; however, the LLA group demonstrated a second TES onset during mid-to-terminal swing that was not observed from the control group. In contrast, LES onset times were earlier for the LLA group than controls. For both TES and LES, the LLA group had activation for a greater percentage of the gait cycle than the controls at most speeds. In addition, those in the LLA group walked with increased frontal plane trunk range of motion and a more in-phase inter-segmental coordination than controls at all speeds.

These data suggest that trunk neuromuscular control strategies in those with LLA are driven by a functional need to proximally generate torque to advance the affected limb; this strategy may increase LBP risk over time.

This effort was supported by the Peer Reviewed Orthopaedic Research Program (PRORP), with strategic alignment to CRMRP/JPC-8, USU, and EACE.

Potential TBI Biomarkers and Therapeutics

White Matter Disintegrity Following Mild Traumatic Brain Injury May Explain Abnormalities in Cognition, Emotion, and Sleep

Researchers from the McLean Hospital (Boston, MA), through a series of cross-sectional studies, aimed to determine whether measures of damage to neuronal pathways following mild traumatic brain injury (mTBI) would explain abnormalities in functional connectivity of the brain, cognition, and emotion and whether these measures could serve as biomarkers of mTBI.

The studies included individuals that had sustained a mTBI and healthy adults. Participants underwent magnetic resonance imaging (MRI) or diffusion tensor imaging (DTI) scans to assess changes in brain structures and functional connectivity. Attention, sleep, and emotion (aggression and depression) were also assessed. Examination of structural changes revealed a thickening of the cortex and a decrease in cortical surface area in mTBI patients during the acute/subacute phase of injury, followed by an increase in cortical thickness in specific regions of the brain in the chronic phase when compared to healthy controls (Figure 7-6; *Bajaj et al., 2018*). Increases in cortical thickness in certain brain areas were associated with decreases in the ability to pay attention.

Studies investigating the relationship between emotion, sleep, and the integrity of specific neuronal pathways showed that self-reported poor sleep quality and depressive symptoms following mTBI were correlated with reduced integrity of neuronal pathways in multiple areas of the brain involved in sleep-wake cycle and emotion regulation, information processing, cognitive control, attention, and executive function (Figure 7-7; *Raikes et al., 2018*). Furthermore, elevated aggression has been noted in adults with chronic mTBI. High levels of aggression were associated with changes in a

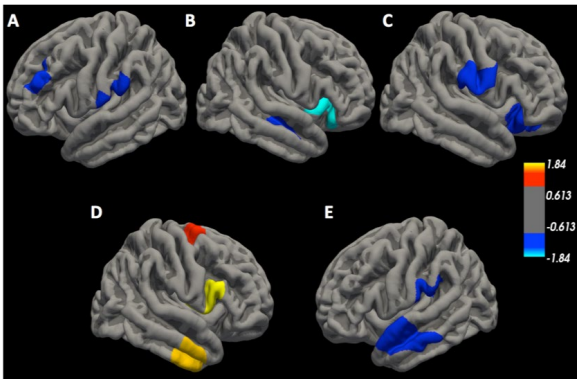


FIGURE 7-6: Compared to healthy controls, we observed thicker cortex within the left hemisphere in mTBI individuals following 3-6 months post mTBI (A), thicker cortex within the right hemisphere in mTBI individuals following 0-3 months post-mTBI (B), and 3-6 months post mTBI (C). However, compared to healthy controls, mTBI individuals had lesser cortical surface area following 3-6 months post mTBI (D). Lastly, cortical surface area was greater following 6-18 months post mTBI compared to 3-6 months post mTBI (D). (*Bajaj, et al., 2018, Human Brain Mapping, 39, 1886-1897*).

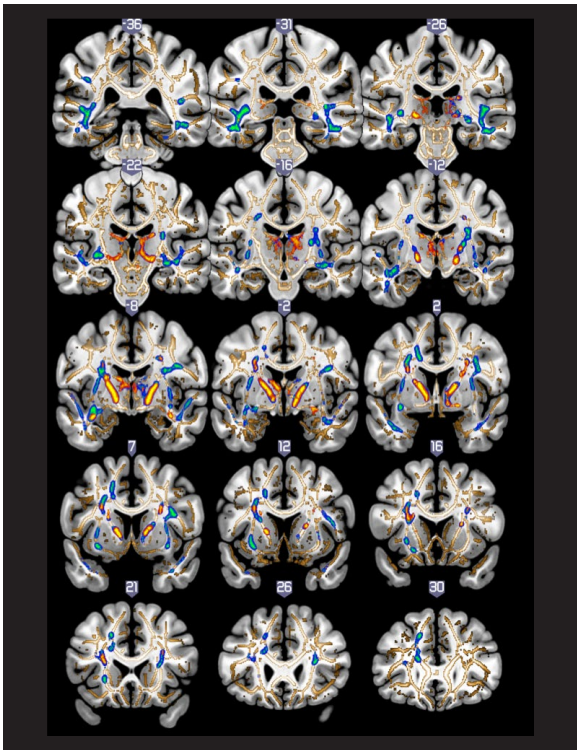


FIGURE 7-7: Whole-brain tract-based spatial statistics correlations with Pittsburgh Sleep Quality Index scores for the mTBI participants overlaid on the average FA skeleton (gold). Significant positive (Radial Diffusivity (RD) = green voxels) and negative (Fractional Anisotropy (FA) = yellow voxels) correlations were observed. Surrounding voxels are filled (FA = red; RD = blue) for visualization purposes. Images are in neurologic orientation (left is left and right is right) and MNI152 space (*Raikes, et al., 2018, Frontiers in Neurology, 9, 468*).

neuronal pathway that connects the two sides of the brain (Figure 7-8; *Dailey et al., 2018*). Imaging also revealed that increased connection between neurons involved in recognizing emotions was associated with higher aggression in individuals with mTBI, but not in healthy controls (Figure 7-9; *Dailey et al., 2018*).

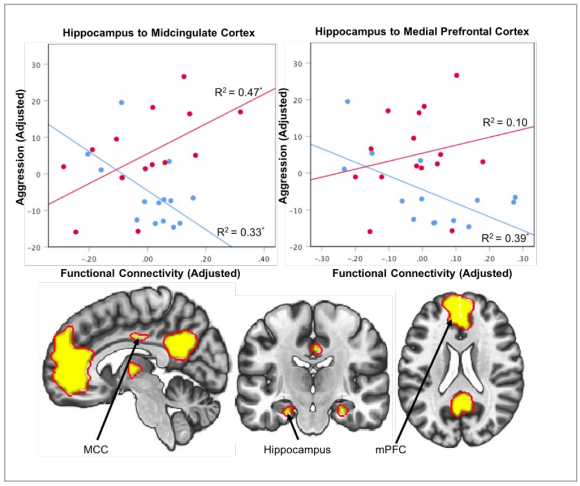


FIGURE 7-8: Significant group differences in ROI-to-ROI connectivity associated with aggression was found from the hippocampus to midcingulate cortex (MCC) and hippocampus to the medial prefrontal cortex (mPFC) (*Dailey, et al., 2018, NeuroReport, 29, 1413-1417*).

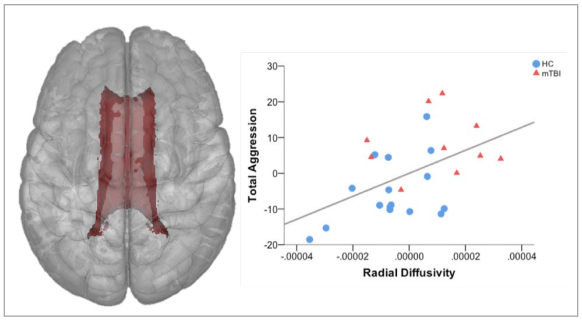


FIGURE 7-9: Corpus callosum shown in red overlaid on a standard brain. The scatterplot shows a significant association between a measure of poor white matter integrity (*i.e.*, radial diffusivity) of the corpus callosum and greater aggression, particularly among those with mild traumatic brain injury (mTBI)(*et al., 2018, Frontiers in Behavioral Neuroscience, 12, 118*).

Taken together, these studies demonstrate the potential of observed changes in the anatomy of the brain which could potentially serve as injury markers to assist in predicting those at risk for prolonged symptoms and protracted recovery.

This effort was managed by CDMRP with support and program oversight by CCCRP/JPC-6.

TBI Endpoints Development Initiative Obtains Regulatory Support for Biomarkers of TBI

Well-defined endpoints and changes to clinical trial design are needed to support successful regulatory-driven development of diagnostics and therapeutics for TBI. This includes advancing the identification, validation, implementation, and dissemination of clinical outcome assessments (COA) and biomarkers for acceptable use in regulatory review of U.S. Food and Drug Administration (FDA)-qualified medical device and drug development tools for mild to moderate TBI. The TBI Endpoints Development (TED) Initiative, a network of public and private partnerships led by scientists at the University of California (San Francisco, CA) seeks to provide the foundational framework for improved clinical trials which can be used to support regulatory approvals for TBI diagnostics and therapeutics.

In January 2018, the FDA issued a second Letter of Support for the TED Initiative's work in advancing the biomarkers glial fibrillary acidic protein (GFAP) and ubiquitin C-terminal hydrolase-L1 (UCH-L1) for use in improved TBI clinical trial design. The TED research group has added to the evidence-base for these biomarkers in recent publications, including a meta-analysis of UCH-L1's diagnostic value and correlation with CT scan results following TBI (*Shahjouei et al., 2018*). From 13 reports across 10 original studies, findings were assessed for risk of bias according to the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) method. Serum UCH-L1 had high accuracy but high risk of bias in predicting CT scan findings. The risk of bias was low for plasma UCH-L1, but the accuracy was only considered moderate in predicting CT scan findings. The authors conclude that further research is necessary to determine whether and how UCH-L1 levels may be used as an alternative to CT scanning.

In addition to advancing work with GFAP and UCH-L1, the TED Initiative is looking at the use of

other blood-based biomarkers such as spectrin breakdown products, neurofilament proteins (for axonal injury), tau (for neurodegeneration), myelin basic protein (for white matter injury), and other potential non-protein biomarkers as theranostic targets for TBI.

This effort was managed by CDMRP with support from PH/TBIRP and programmatic oversight by CCCRP/JPC-6.

Developing a Blood Test for Brain Injury

Head CT scans are currently the standard evaluation method for traumatic intracranial injuries. However, the potential for adverse radiation exposure, high cost and unnecessary use of resources, and limited utility for mTBIs have led to exploration of other solutions to diagnose and evaluate mTBI in Service members. Researchers at Banyan Biomarkers (San Diego, CA) performed a clinical trial to validate two brain-specific protein markers that rapidly appear in the blood after TBI, ubiquitin C-terminal hydrolase-L1 (UCH-L1) and glial fibrillary acid protein (GFAP), as potential biomarkers for intracranial injury. The study design involved recruitment of patients admitted to emergency departments with suspected TBIs that also received a CT scan and blood withdrawal within 12 hours of injury. The serum was analyzed for concentrations of UCH-L1 and GFAP. Patients with concentrations above a defined threshold were considered positive for traumatic intracranial injuries. The study found that while only six percent of patients with a TBI (determined by Glasgow Coma Scale scoring) had injuries detected by CT, 66 percent were found to be positive for the UCH-L1 and GFAP test. The test had a sensitivity of 0.976 and a negative predictive value of 0.996 for detection of intracranial injuries. These efforts have resulted in the development of the Banyan Biomarkers BTI™ brain trauma indicator assay. After an injury, the assay can identify UCH-L1 and GFAP concentrations in the blood. Medical professionals can use this objective information to evaluate patients with suspected mild TBI, potentially reducing the need for CT scans.

The U.S. Food and Drug Administration (FDA) approved Banyan Biomarkers to market their Brain Trauma Indicator (BTI™) brain trauma indicator assay. This is the first FDA-authorized blood test for TBI and concussions.

This effort was supported by the U.S. Army and the Defense Health Program.

Developing a Framework for the Evaluation of TBI Therapeutics and Identification of New Clinical Biomarkers

The Operation Brain Trauma Therapy-Extended Studies (OBTT-ES) is an extension of the paradigm-shifting Operation Brain Trauma Therapy (OBTT), a multi-site consortium consisting of investigators from University of Miami School of Medicine (Miami, FL), Walter Reed Army Institute of Research (WRAIR; Silver Spring, MD), Virginia Commonwealth University (Richmond, VA), Banyan Biomarkers, Inc (San Diego, CA), University of Florida (Gainesville, FL), University of Pittsburgh School of Medicine (Pittsburgh, PA) and University of Messina (Messina, ITL). OBTT uses a collaborative approach to systematically evaluate TBI therapeutics in preclinical animal models.

Ultimately, OBTT and OBTT-ES aimed to (1) identify agents that can easily transition to clinical trials or be further evaluated clinically in a precision medicine approach to explore domains of benefit (*e.g.*, cognition, motor, lesion size) identified in preclinical models, and (2) identify cross-model assessment biomarkers that correlated with standard outcomes.

OBTT and OBTT-ES uses a two-tier system to identify candidate therapeutics. Outcomes from the evaluations were scored using a unique 22-point system that considers the differences between the models and evaluations performed. The first tier uses established models of

controlled cortical impact, penetrating ballistic-like brain injury, and parasagittal fluid percussion TBI models in rodents. Agents that perform well advance to a second tier that features larger animal models and more complicated models (*e.g.*, the inclusion of hemorrhagic shock) that mimic the battlefield experience. Of the 12 drugs that have completed testing, levetiracetam and glibenclamide have performed the best. Levetiracetam is a U.S. Food and Drug Administration (FDA) approved antiepileptic that showed the most benefit in mild TBI models. Glibenclamide, an FDA approved anti-diabetic drug, showed the most benefit in the cerebral contusion models.

The OBTT and OBTT-ES represent a research paradigm that could be used for the pragmatic evaluation of pre-clinical drugs for the treatment of neurological diseases and conditions.

This effort was managed by CDMRP with support from PH/TBIRP and programmatic oversight by CCCRP/JPC-6.

Complement System Targets and Models

Complement Inhibition Ameliorates Blast-induced Acute Lung Injury in Rats

Complement is a network of proteins in the plasma that target and mark pathogens in the body for destruction by other immune processes. Complement inhibition by protein decay-accelerating factor (DAF) was found to protect the brain from blast-overpressure (BOP)-induced damage (*Li et al., 2013*). Thus, researchers at U.S. Army Institute of Surgical Research (USAISR; Fort Sam Houston, Texas) conducted a study to determine the effect of DAF on acute lung injury induced by BOP exposure and to elucidate its possible mechanisms of action (Figure 7-10). BOP exposure significantly increased the production of pro- and anti-inflammatory proteins (cytokines), and pathological changes such as swelling of the lungs, inflammation, blood vessel damage, and hemorrhage in the lungs (Figure 7-11). These alterations were ameliorated by early administration of DAF (Figure 7-12). The DAF treatment significantly reduced the levels of pro-inflammatory and complement proteins HMGB1, RAGE, NF-[κ]B, C3a, and C3aR and reversed HMGB1 and complement protein C3a activities

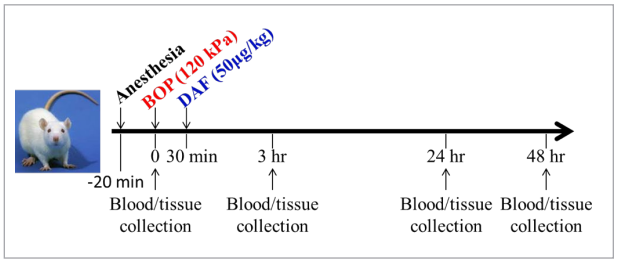


FIGURE 7-10: Experimental design and timeline.

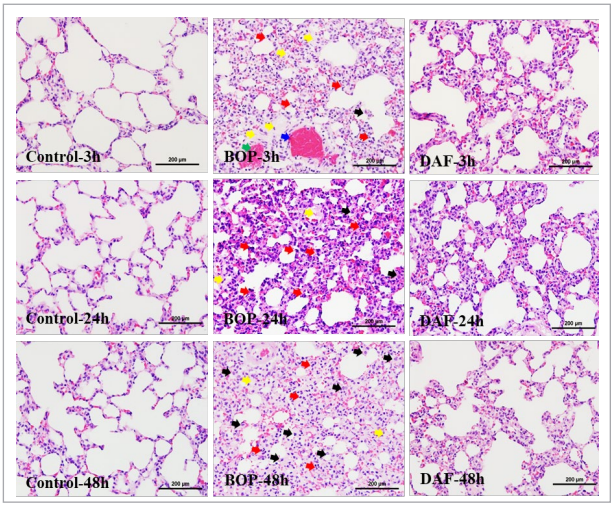


FIGURE 7-11: DAF treatment mitigated lung tissue injury induced by BOP in a rat model.

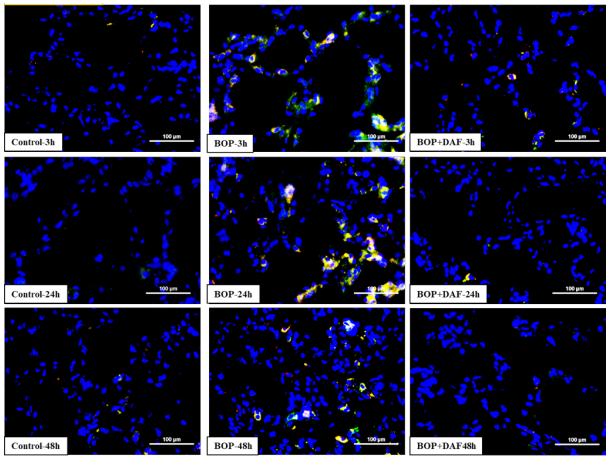


FIGURE 7-12: Effect of DAF on interaction of C3a and C3aR in lungs of rats after BOP exposure.

(Figure 7-13). These findings indicate that early administration of DAF efficiently inhibits systemic and local inflammation and mitigates blast-induced lung injury. The underlying mechanism might be attributed to its potential modulation of C3a and HMGB1. Therefore, complement and/or HMGB1 may be potential therapeutic targets in amelioration of acute lung injury after blast injury.

This effort was supported by the DMRDP.

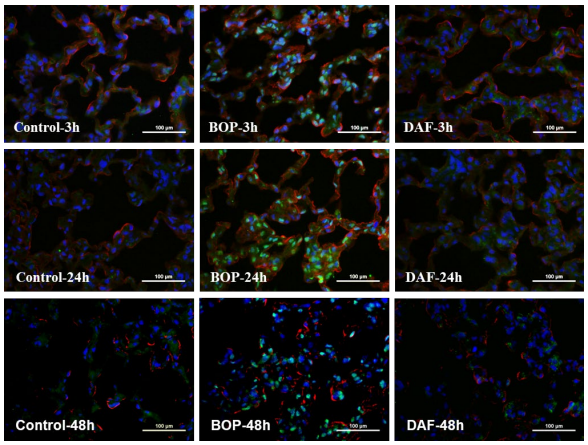


FIGURE 7-13: Effect of DAF on HMGB1 and RAGE expression and translocation in rats exposed to BOP.

Clinical Impact of Early Complement Activation in Combat Casualties with Blast Injury

The complement system plays a role in the early response to injury and is involved in the pathogenesis of subsequent organ failure. Researchers at U.S. Army Institute of Surgical Research (USAISR; Fort Sam Houston, TX) investigated the relationship between the complement system and clinical variables in combat casualties with blast injury. Service members sustaining blast trauma during Operation Iraqi Freedom (OIF) were included in the study (n = 54). Levels of complement factors were measured in sera from samples drawn at admission and 8 and 24 hours later. Results were compared to levels of complement factors in healthy controls (n = 10).

Levels of complement factors C5b-9, Bb, and C4d were significantly higher in the injured group than in controls at all time points, while levels of C5a were significantly higher in the injured group than in controls initially and 8 hours after admission (Figure 7-14). Complement factors were significantly correlated with multiple clinical variables including injury severity score, Glasgow Coma Scale, and infusion of crystalloids and colloids. C5a and C5b-9 were positively correlated with Bb but not C4d at admission and 8 hours later, suggesting that the alternative complement pathway, but not the classic or lectin complement pathways, contributed to early complement activation (Figure 7-15). However, C4d was inversely correlated with mortality, suggesting that the classical or lectin complement pathway may play a protective role in this setting.

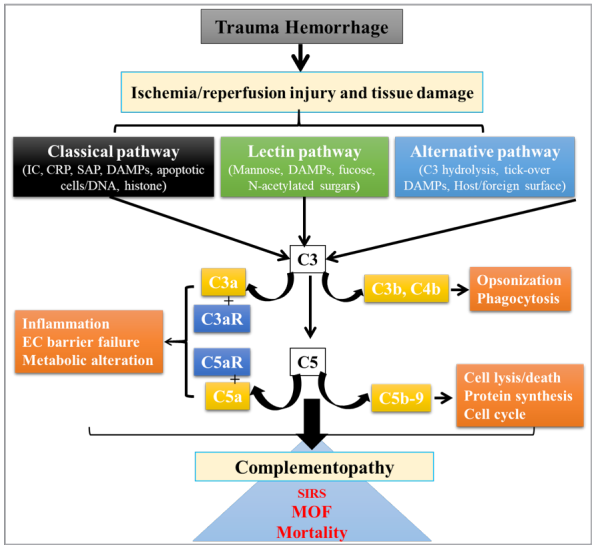


FIGURE 7-14: Schematic model and proposed roles of complement activation in traumatic hemorrhage. C3aR, C3a receptor; C5aR, C5a receptor; CRP, C-reactive protein; DAMPs, damage-associated molecular patterns; EC, endothelial cell; IC, immune complex; MOF, multiple organ failure, SAP, serum amyloid P; SIRS, systemic inflammatory response syndrome.

These data demonstrated that acute complement and inflammatory responses were present in military blast trauma patients and correlated with clinical variables of importance. They reinforce previous findings that early therapeutic

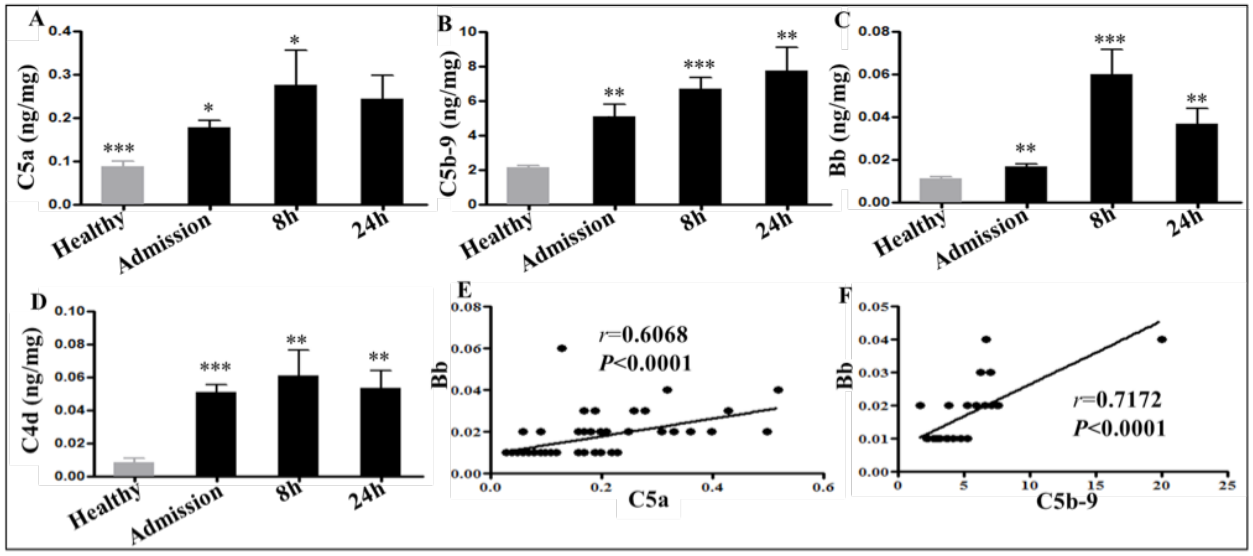


FIGURE 7-15: Systemic activation of complement and alternative complement pathways in military casualties with blast injury. A-D, Plasma levels of C factors of C5a, C5b-9, Bb and C4d were measured by ELISA in healthy donors (n=10) and trauma patients at admission (n=54), 8 hr (n=23)and 24 hr (n=9) after admission. E-F, correlation between alternative pathway (Bb) and C5b-9 in the injured patients at admission. The data were expressed as nanogram per milligram plasma protein and presented as mean ± SEM, * p<0.05. ** p<0.01, *** p<0.001 vs. healthy.

modulation of the complement system may reduce morbidity and mortality in trauma patients.

This effort was supported by CCCRP/JPC-6.

Development of a Clinically Relevant Trauma Model for Evaluation of Complement Inhibitors

Development of complement inhibitors for trauma management requires appropriate animal models that recapitulate the immunological and pathophysiological processes experienced by humans. To address this need, researchers at U.S. Army Institute of Surgical Research (USAISR; Fort Sam Houston, TX) have developed a clinically relevant rat model of blast injury and hemorrhagic shock.

In their model, rats were exposed to 116 kPa overpressure then immediately experienced a 50 percent blood loss. After a 30-minute period they were provided fluid resuscitation and observed. Levels of complement factors were measured in blood drawn at each step of the injury model.

The combined injury protocol resulted in multiple organ damage, hemorrhagic shock, a high mortality rate (70 percent), metabolic acidosis, and hyperkalemia. Levels of C1q, C3, and plasminogen were significantly lower

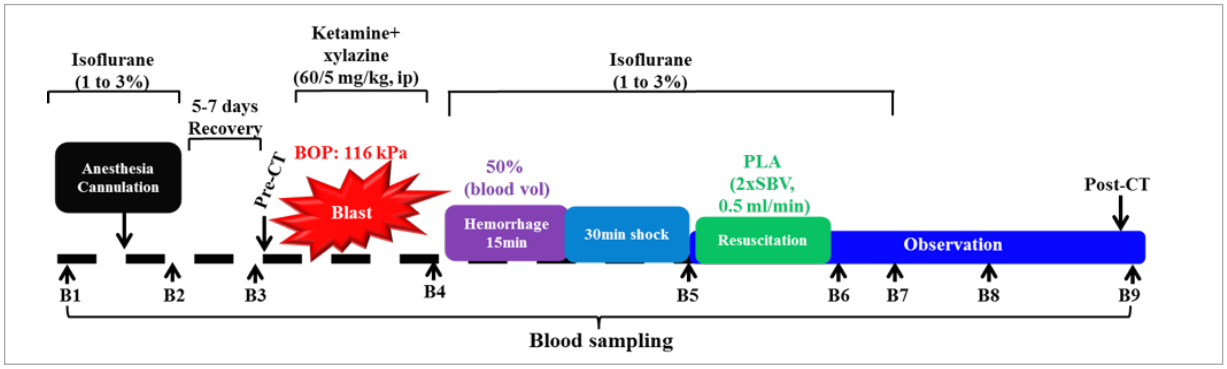


FIGURE 7-16: Experimental design and timeline.

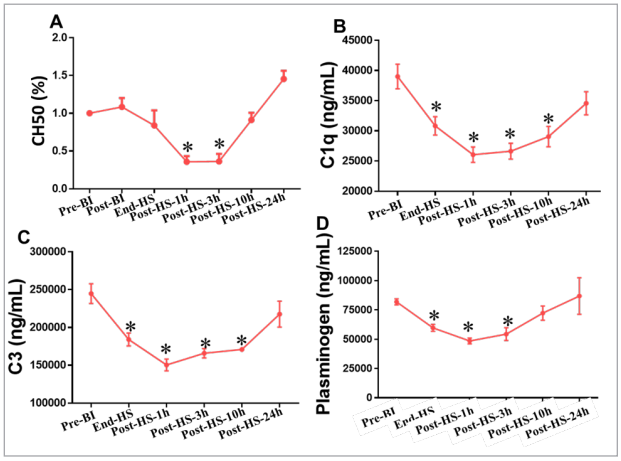


FIGURE 7-17: Complement activation/consumption in rats after blast injury and hemorrhagic shock. The hemolysis activity (CH50, A), complement components of C1q (B), C3 (C), plasminogen (D) were determined by ELISA. The data are expressed as mean ± SEM, and comparison was performed by two-tailed unpaired t test with Welch's correction: * p<0.05, individual time points vs. Pre-BI.

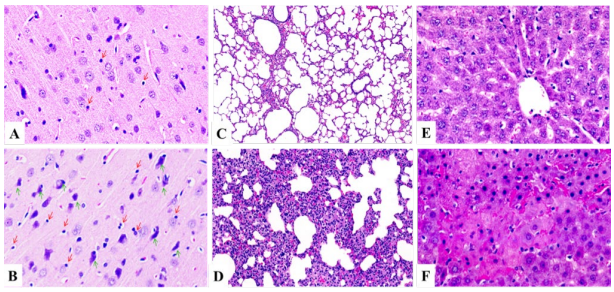


FIGURE 7-18: Multiple organ damage after blast injury and hemorrhagic shock in rats. Tissue histological alterations were evaluated in H&E-stained paraffin slide. Compared to the sham (A), injury in gray layer of cerebral cortex showed neuronal apoptosis and microglial infiltration (B). The representative photomicrographs were shown with the lung damage characterized by inflammatory infiltration, septal thickening, and hemorrhage (D) when compared with the sham (C). C, the liver damage characterized by hepatic nuclear condensation, coagulation necrosis and inflammatory infiltration (F) compared with the sham (E).

immediately after shock through 3 hours of follow up than at baseline, but differences were no longer significant after 24 hours (Figures 7-16, 7-17, and 7-18). This combined trauma model mimics clinical immune physiology and complementopathy and will provide a valuable platform for testing the efficacy of immune modulators, such as complement inhibitors, following trauma.

This effort was supported by USAMRMC and is strategically aligned with CCCRP. The award is managed by DHA.

HMGB1 Release is Associated with Clinical Outcomes After Blast Injury

High mobility group box 1 (HMGB1) is a key damage-associated molecular pattern that mediates inflammation and contributes to multi-organ failure after injury. In this study, researchers at U.S. Army Institute of Surgical Research (USAISR; Fort Sam Houston, TX) investigated HMGB1 levels and determined their correlation with mortality in Service members and rats with blast-related trauma (Figure 7-19).

Levels of HMGB1 in Service members with blast-related trauma (n = 54) were significantly higher than levels in healthy controls (n = 10) at admission and 8 hours later, but the difference was no longer significant at 24 hours. Levels of HMGB1 were significantly correlated with clinical variables including injury severity score; Glasgow Coma Scale; systemic inflammatory response syndrome;

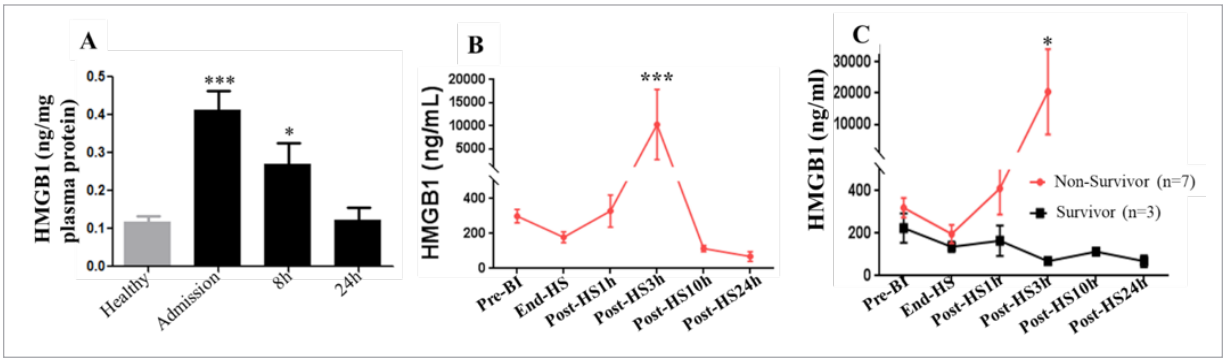


FIGURE 7-19: (A) early HMGB1 release in Service members with blast injury. * p < 0.05, and *** p < 0.001 vs. healthy controls. Increased blood levels of HMGB1 (B) were associated with mortality in rats subjected to blast injury and 50% hemorrhage (C). * p < 0.05 vs. non-survivor.

infusion of RBC, crystalloids, and FFP; and levels of complement factors C3a, C5a, and Bb. In a rat model of blast exposure (116 kPa) and subsequent 50 percent hemorrhage (n = 10), levels of HMBG1 were significantly higher 3 hours after injury than at baseline but returned to pre-injury levels by 10 hours after injury. Levels of HMBG1 were significantly higher in non-surviving than surviving rats at the 3-hour time point (n = 7 and 3, respectively).

These results demonstrate that HMGB1 is expressed in the acute phases of blast injury and HMGB1 levels correlated with clinical outcomes. Thus, HMGB1 may be a promising diagnostic and therapeutic target in trauma patients.

This effort was supported by USAMRMC and is strategically aligned with CCCRP. The award is managed by DHA.

Early Inhibition of Complement C5 Significantly Reduces Mortality and Protects Against Multi-Organ Failure in a Clinically Relevant Model of Blast Injury and Severe Hemorrhage

Trauma-induced hemorrhagic shock is a leading cause of death for military casualties and civilian trauma patients. Researchers at U.S. Army Institute of Surgical Research (USAISR; Fort Sam Houston, TX) previously demonstrated that early complement terminal pathway activation was present in rats exposed to blast overpressure (BOP) and correlated with clinical outcomes in Service members with blast-related trauma. They have also recently evaluated the efficacy of a complement C5 inhibitor, Coversin, on survival and multi-organ damage in an animal model of blast injury and severe hemorrhagic shock.

Early treatment with Coversin led to full complement inhibition within 10 hours and sustained inhibition for up to 24 hours (Figure 7-20). Animals treated with Coversin had significantly lower mortality, less metabolic acidosis, and better response to fluid resuscitation than untreated controls (Figure 7-21). In addition, Coversin significantly mitigated damage to brain, lung, and liver tissue.

These data demonstrate that complement C5 inhibition during the acute phase of injury could be

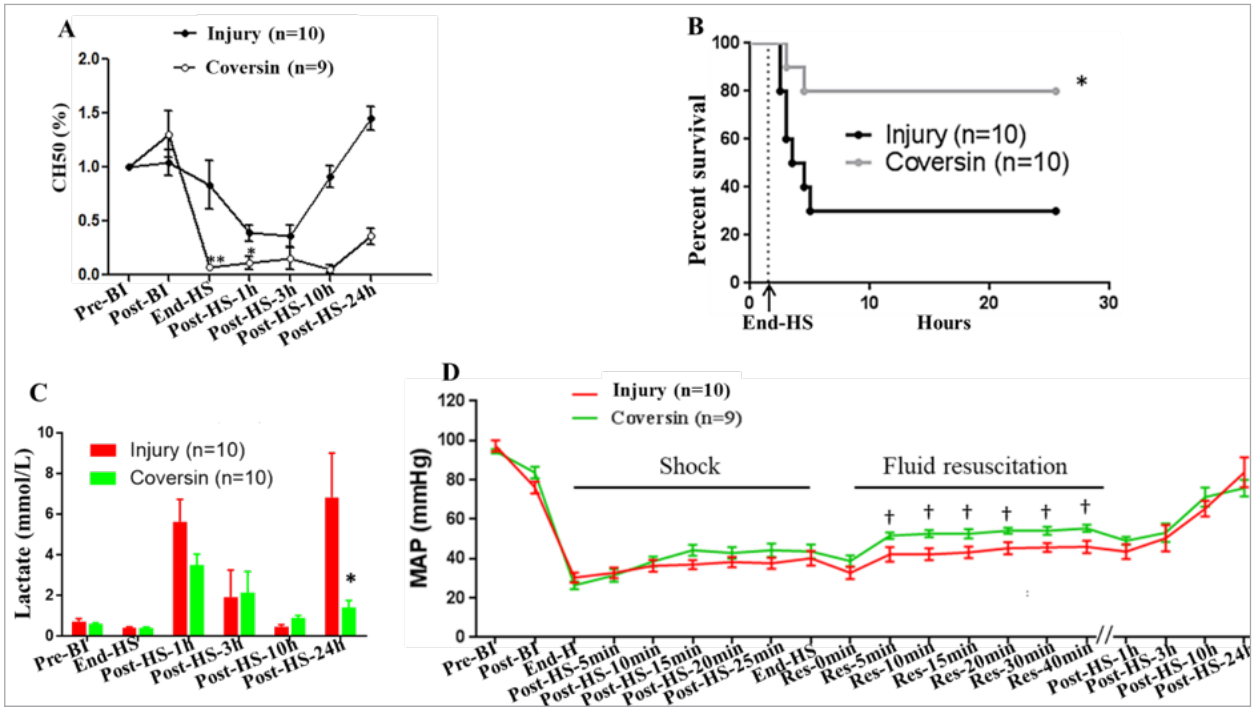


FIGURE 7-20: Complement C5 inhibitor (Coversin) treatment significantly inhibits complement activation (A), increased survival (B), reduced acidosis (C), and elevated blood pressure (D).

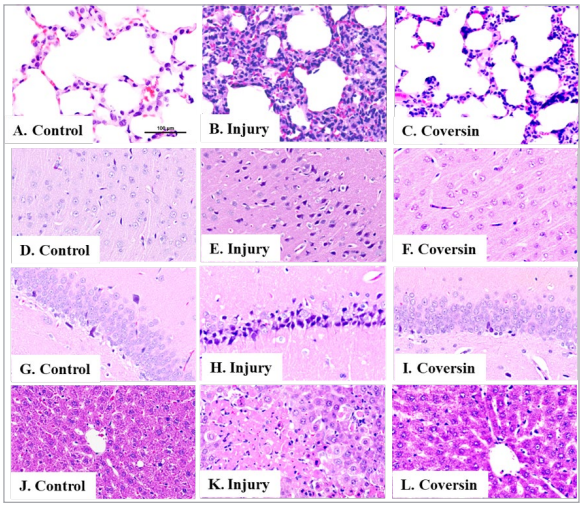


FIGURE 7-21: Effect of Coversin on lung injury (A-C), brain cortex (D-F), brain hippocampal injury (G-I), and liver injury (J-L), in a rat model of blast Injury and hemorrhage. Tissues were collected and fixed in 10% formalin solution. Tissue damages were evaluated by H&E staining.

an important therapeutic approach to protect against multi-organ failure and improve survival after blast-related trauma. Using a C5 inhibitor in the pre-hospital setting may lead to a significant reduction in morbidity and mortality of Service members and civilians who suffer traumatic hemorrhage.

This effort was supported by USAMRMC and is strategically aligned with CCCRP. The award was managed by DHA.

Spinal Cord Injuries

Presence of Motor Evoked Potentials in Patients with Severe Spinal Cord Injury as a Prognostic Marker to Predict Neurological Improvement

Motor evoked potentials (MEP) are electrical signals that can be recorded in the muscles and spinal cord in response to activity in the motor centers of the brain. These signals can be disrupted after traumatic spinal injury; however, it is unclear what relationship exists between the presence or absence of these signals after injury and clinical neurological function. In this study, researchers at the University of California (San Francisco, CA) performed a retrospective chart review to evaluate the diagnostic and prognostic value of MEP status in patients with acute spinal cord injury (SCI).

The study revealed that MEP presence predicted neurological function, as measured by American Spinal Injury Association Impairment Scale (AIS), at discharge. Patients with present MEPs had higher AIS grades (indicating less impairment) at discharge in comparison to patients with absent MEPs. Additionally, in patients with more severe SCI (*i.e.*, AIS A-C), the degree of neurological recovery was greater in patients with MEPs vs. those without. Finally, MEP presence also correlated with degree of SCI as measured by MRI and Brain and Spinal Injury Center (BASIC) scoring (*Dahll et al., 2018*).

As a whole, this study supports MEP status as a diagnostic of neurological and neurophysiological injury as well as a predictor of neurological recovery.

This effort was supported by SCIRP and strategically aligned to CRMRP/JPC-8.

Identifying Therapeutic Targets to Aid in the Recovery of Respiration Post-cervical Spinal Cord Injury

Cervical spinal cord injury (SCI) results in a range of long-term deficits, one of which is impaired respiration, which results in a need for assisted ventilation. Impairment is largely due to damage to the phrenic neural pathways, the connections between neurons that controls the diaphragm. Through a series of studies, researchers at Drexel University (Philadelphia, PA) investigated changes in the phrenic circuitry after SCI and explored potential therapeutic targets for improved respiratory function among the cervical SCI population.

Specific spinal neurons known as interneurons have been shown to promote changes in respiratory pathways. In the first study, the team investigated whether transplantation of interneurons may

Photo credit: Spc. Hubert D. Delany III/ U.S. Army

improve respiratory outcomes after SCI. Rats with upper SCIs received grafts of dissociated, developing spinal cord tissue (tissue abundant in interneurons) from a healthy rat pup. After one month, neurons from the donor had formed connections with host phrenic neurons. Connections from host neurons onto donor neurons were also formed. At this early stage, the anatomical and functional results varied across individuals. However, the results demonstrate significant plasticity of the phrenic circuitry, providing an attractive therapeutic target to aid in weaning individuals off artificial ventilation (*Spruance et al., 2018*).

As demonstration of this therapeutic potential, the team stimulated the tissue around the spinal cord at the level of the phrenic neural center in a rat model of cervical SCI to stimulate breathing and to investigate methods for pacing this circuit (*Bezdudnaya et al., 2018*). High frequency stimulation of the C4 spinal segment was able to maintain breathing. Stimulation also facilitated changes in the timing of nerve signaling suggesting that it may be a potential target for pacing phrenic activity.

Additional research from this group investigated factors contributing to spontaneous recovery of diaphragm function following SCI (*Bezdudnaya et al., 2018; Hormigo et al., 2017*). It was determined that anesthesia attenuates recovery, suggesting that the N-methyl-D-aspartate (NMDA) neuronal receptors that are suppressed by anesthesia are critical for respiration and are potential therapeutic targets (*Bezdudnaya et al., 2018b*).

Therapies acting on the targets identified in this work could aid in weaning patients with spinal cord injury and resulting respiratory dysfunction off an artificial ventilation system.

This effort was supported by SCIRP and strategically aligned to CRMRP/JPC-8.

Vision System Injury Repair and Mitigation

CB2 Receptor Action of the FDA-approved Drug Raloxifene Mitigates Visual Deficits and Visual System Pathology after Mild TBI

Visual deficits after traumatic brain injury (TBI) are common, but interventions that limit post-trauma impairments have not been identified. A

recent study found that treatment of closed-head blast TBI with the cannabinoid type-2 receptor (CB2) inverse agonist SMM189 greatly attenuates the visual deficits and retinal pathology produced by mTBI in mice, by modulating the otherwise deleterious role of microglia in the injury process after trauma (*Reiner et al., 2015*). SMM189 is, however, not yet approved for human use, and is years away from the regulatory approval needed for therapeutic use in humans. Raloxifene is, however, an FDA-approved estrogen receptor drug used to treat osteoporosis that was recently found to also show noteworthy CB2 receptor inverse agonism. Given its FDA-approved status as safe for human use, raloxifene could potentially be used to treat TBI in humans.

Researchers at the University of Tennessee Health Science Center (Memphis, TN) sought to determine if raloxifene can reduce visual system injury and dysfunction after mTBI. In a comprehensive series of functional and morphological studies, raloxifene was injected intraperitoneally at either a low (5 mg/kg) or high (10 mg/kg) dose 2 hours after TBI. Deficits in contrast sensitivity and visual acuity; reductions in the electrical activity from the retina; and increases in anxiety, light aversion, and pupil constriction in response to light were evident when functional tests were performed months after the blast. These negative outcomes of blast TBI were completely or nearly completely remedied by two weeks of raloxifene treatment, with the higher dose generally being more effective. Raloxifene also rescued the loss of axons in the optic nerve and neurons in the oculomotor nucleus following the blast, and normalized an increase in retinal ganglion cell melanopsin, a pigment that mediates light aversion and pupil constriction. Raloxifene treatment was still effective even when delayed until 48 hours after TBI. In studies examining non-visual deficits after TBI, the same researchers at the University of Tennessee Health Science Center also found that fearfulness and anxiety caused by closed-head blast TBI in mice was mitigated by raloxifene.

The effects of raloxifene appear attributable to its CB2 inverse agonism rather than its estrogenic actions and are driven by a biasing of microglia after blast TBI from the harmful pro-inflammatory M1 state to the pro-healing M2 state. Due to its action at CB2 receptors, raloxifene effectively mitigates visual system injury and dysfunction after head trauma in mice and could be rapidly repurposed for use in humans for treatment of TBI (Figure 7-22).

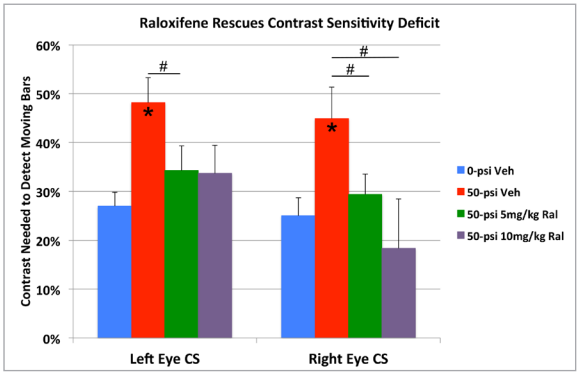


FIGURE 7-22: Contrast sensitivity as measured using Optometry in sham blast and blast mice receiving vehicle, and blast mice receiving raloxifene at either 5 mg/kg or 10 mg/kg. The contrast needed to detect moving stripes was significantly greater for both eyes in blast-vehicle (asterisk) than in sham mice. Contrast sensitivity in the 5 mg/kg raloxifene mice was significantly better than in the blast mice with vehicle for both eyes (bars with pound signs), and for the right eye in the case of 10 mg/kg raloxifene (bar with pound sign). (*Dente et al., 2010*).

This effort was managed by CDMRP with support from PH/TBIRP and programmatic oversight by CRMRP/JPC-8.

Maresin 1 (MaR1) Reduces Glial Cell Damage in Retina Injury Induced by Blast Wave Exposure

Maresin 1 (MaR1), one of a group of unique signaling molecules called specialized pro-resolving lipid mediators (SPMs) has been shown to attenuate the induction and accumulation of harmful mediators that lead to neuronal cell death in several neurodegenerative disease models (*Serhan, 2015*). To elucidate the role of

MaR-1 in retinal cell survival following blast injury, researchers at the U.S. Army Institute of Surgical Research (USAISR; San Antonio, Texas) conducted a multi-phase study to validate a blast eye injury model and determine the acute (48 hours post injury) effects of MaR1 on structural changes in the retina after blast wave exposure. A compressed-air driven shock tube was used to expose anesthetized rats to shock waves simulating an open-field blast exposure. Approximately 30 minutes after exposure, the rats were treated with MaR-1, or a control intravenously. Unexposed rats were included as controls. Retinal tissue was collected and analyzed for relative levels of glial fibrillary acidic protein (GFAP), an indicator of damage to brain cells called glia (gliosis).

The results indicate that there is an increase in the level of GFAP throughout the retina of blast-exposed rats as compared to controls (Figure 7-23A), indicating that blast exposure induces retinal damage manifested as increased levels of GFAP. However, blast-exposed rats treated with MaR-1 showed a dose-dependent reduction in GFAP levels (Figure 7-23B) which suggests that MaR-1 intervention curbs increases in glial damage proteins (*Rios et al., 2018*). Thus, treatment with MaR-1 may provide an effective strategy to reduce or halt retina glia cell damage resulting from primary blast exposure. These findings introduce a target for pharmaceutical intervention and clinical translation for the protection of vision in the warfighter after exposure to explosive devices in combat.

This effort was supported by the USAMRMC, CRMRP, MOMRP, and the National Research Council Research Associate Program and the Oak Ridge Institute for Science and Education (ORISE).

Anti-infective Studies

Nanoemulsion Formulations (NB-201) Provide an Effective Topical Antimicrobial for Methicillin-resistant Staphylococcus Aureus in an Infected Pig Burn Wound Model

The leading cause of combat-related morbidity and mortality is complications due to infection (*Blyth et al., 2015*). These infections can occur due to delays in treatment in the field,

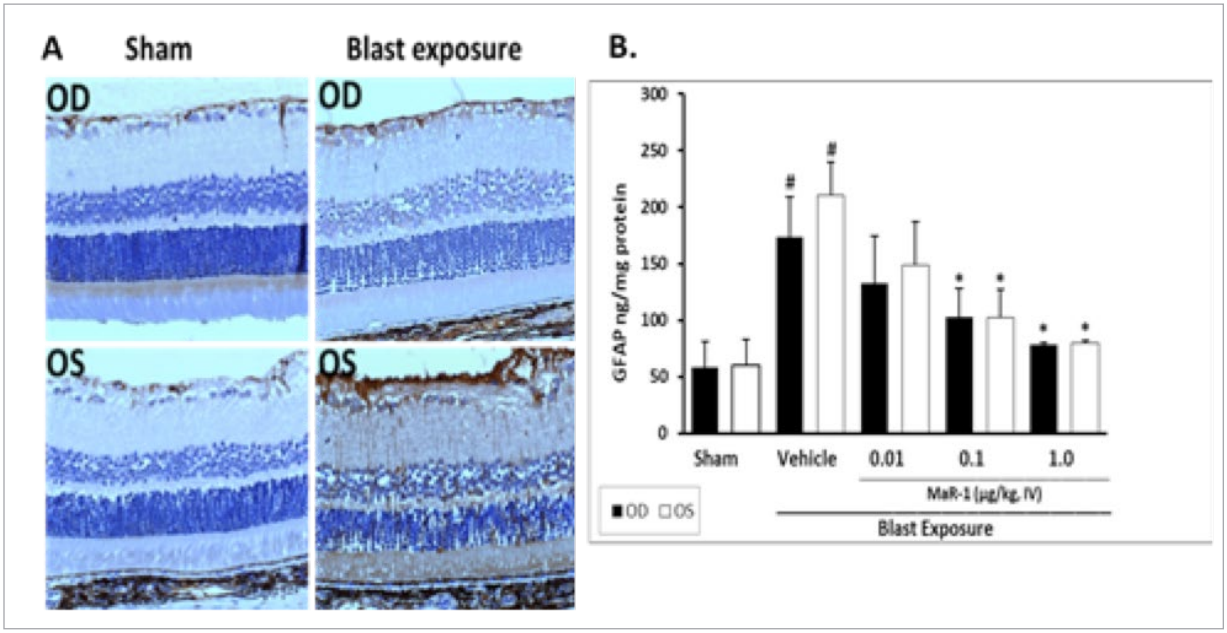


FIGURE 7-23: GFAP expression in retinal tissues after blast exposure. (A) Increasing GFAP levels with blast exposure. (B) MaR1 reduced GFAP levels in the retina after blast exposure. (Figure used with permission from the authors)

invasive surgeries, or hospitalization (*Rex, 2012*). These risk factors are compounded by the increasing prevalence of antibiotic-resistant microorganisms, so the need for an antimicrobial treatment that could be utilized in a variety of settings against antibiotic-resistant organisms is imperative.

To meet this unmet need, researchers at the University of Michigan (Ann Arbor, MI) developed a nanoemulsion (NB-201) as an antimicrobial agent for treating antibiotic-resistant wound infections.

In previous work done for this project, NB-201 was shown to be an effective treatment against methicillin-resistant Staphylococcus aureus (MRSA) in an abraded porcine wound model (*Cao et al., 2017*).

Building upon the success of this study, the effectiveness of NB-201 against MRSA infected porcine burn wounds was initiated. As a part of this investigation, a porcine infected burn wound model was developed. Once an infected burn wound procedure was established, the effectiveness of NB-201 treatment against MRSA infected burn wounds was investigated and compared to an NB-201 placebo. The samples collected were tested under two conditions, MRSA selected and non-selected plating conditions. The NB-201 treated wounds showed a significant decrease in colony-forming units (CFUs), for both testing conditions, when compared to the NB-201 placebo. These results show that the NB-201 nanoemulsion is an effective treatment against MRSA infected burn wounds (Figure 7-24).

Three NB-201 formulations have been manufactured under current Good Manufacturing Practices (cGMP). All formulations were found to be stable for 12 months at 4 and 25 degrees Celsius and 6 months at 40 degrees Celsius. Additionally, a Good Laboratory Practices (GLP) acute rabbit skin irritation study showed that all formulations tested were found to be non-irritants.

The results from these studies have put NB-201 closer to clinical applications. The development of NB201 as a treatment for antibiotic-resistant wound infections for Service members could aid in decreasing combat-related morbidity or mortality rates.

This effort was managed by CDMRP with support and program oversight by MIDRP/JPC-2.

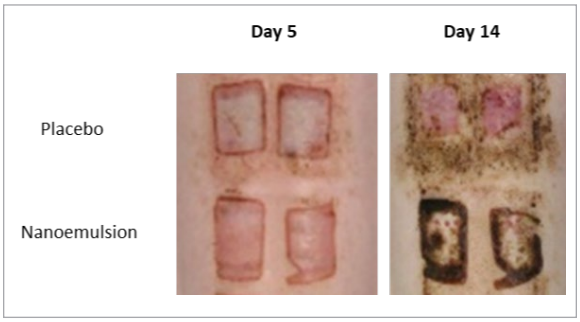


FIGURE 7-24: Infected burn wounds are treated with Nanoemulsion or Placebo. (Figure used with permission from the authors)

Novel Antimicrobial Peptides as Topical Anti-infectives Against Combat-related Bacterial and Fungal Wound Infections

Therapeutic interventions for ballistic wound infections (BWIs) are limited by the increasing number of multidrug resistant pathogens, antibiotic/antimycotic side effects and poor wound penetration. Thus, investigators at Riptide Biosciences, Inc. (Mare-Island-Vallejo, CA) developed designed antimicrobial peptides (dAMPs) to address the challenges present in the treatment of BWIs (*D'Avignon et al., 2008; Horvath EE, et al., 2007*).

dAMPs are based on naturally occurring antimicrobics. Over 30 dAMPs were synthesized and evaluated for their antimicrobial potency against several bacterial and fungal strains. Time-kill assays against bacteria *Pseudomonas aeruginosa* (*P. aeruginosa*) and *Staphylococcus*

Photo credit: Tech. Sgt. Gregory Brook/U.S. Air Force

aureus (*S. aureus*) were utilized as an early screen for microbial reduction by the peptides. Promising dAMPs were then evaluated to determine the lowest concentration required to inhibit growth of the strains. The time-kill assays illustrated that the dAMPs successfully destroy pathogens, and toxicity assays demonstrated that therapeutic levels were not toxic (*Clemens et al., 2017*). The curative potential of three dAMPs (RP504, RP554, and RP557) was evaluated in a pig burn wound model infected with *P. aeruginosa* and *S. aureus* with RP557 yielding remarkable activity. RP557 is now entering Investigative New Drug (IND)-enabling studies.

The clinical implementation of dAMPs could be an innovative method of dealing with antibiotic resistance while providing a new broad-spectrum treatment against biofilms, fungi, and drug-resistant bacterial and fungal infections associated with BWIs, thus reducing the chances for systemic and fatal infections in patients.

This effort was managed by CDMRP with support and program oversight by MIDRP/JPC-2.

Bioengineering

The Human Acellular Vessel for Vascular Repair in Injured Extremities

Researchers from Humacyte, Inc. have developed a human tissue-engineered vascular prosthetic called the Human Acellular Vessel (HAV). The HAV was designed to improve long term patency and drastically reduced rates of infection. HAV is a small, acellular graft made of proteins grown from cultured human cells. The HAV transforms into a

fully functioning vessel by recruiting the patient's own stem cells to replicate host vessel structure and function within four to six weeks. It can be stored at 4 degrees Celsius for use at the point of care, making it amenable to deployment as far forward as Required Operational Capability (ROC) levels two and three.

The current development strategy aims to obtain a primary indication for hemodialysis - a therapeutic area with a clear unmet need and a suboptimal standard of care. Humacyte is conducting a phase two clinical trial at six centers—Johns Hopkins University and University of Maryland Shock Trauma (Baltimore, MD), Grady Memorial Hospital (Atlanta, GA), Rocky Mountain Regional Trauma Center (Denver, CO), Rutgers University (Camden, NJ), and Ryder Trauma Center (Miami, FL). Up to 20 vascular trauma subjects are currently enrolled in the study.

This effort is supported by USAMMDA-Combat Trauma and Acute Rehabilitation Project Management Office.

Avance Nerve Graft Plus Autologous Bone Marrow for Peripheral Nerve Repair
Peripheral nerve injury can have devastating effects on recovery following blast injury. The Avance nerve graft (Axogen, Inc.), an implantable nerve guide that aids in the repair of traumatic peripheral nerve injuries with significant defects, may provide an effective way to quickly mitigate injury damage. This results in less burden to wounded warriors in the short term by lessening length of rehabilitation, and in the long term by reducing recidivistic chronic ailments. The effectiveness of the nerve graft in improving damage after injury is currently being investigated by Walter Reed National Military Medical Center (WRNMMC; Bethesda, MD) and the Curtis National Hand Center (Baltimore, MD). Enrollment of 12 participants is underway.

This effort is supported by USAMMDA-Combat Trauma and Acute Rehabilitation Project Management Office.

Blast Injury Outcomes

Laryngotracheal and Esophageal Trauma Outcomes from Military Operations in Afghanistan, Iraq, and Syria, 2001–2018
Laryngotracheal and esophageal trauma present military providers with especially difficult life-threatening challenges. The airway is often unstable and vascular control is a concern; immediate action is paramount. However, there is no agreement on treatment algorithms for such injuries. Thus, researchers at the Naval Health Research Center (NHRC) and Naval Medical Center (San Diego, CA) investigated the types of laryngotracheal, esophageal, and soft tissue injuries of the neck in a deployed combat setting and described related mortality and length of hospitalization outcomes.

A total of 254 Service members who sustained laryngotracheal and esophageal injuries while deployed were identified from NHRC's Expeditionary Medical Encounter Database (EMED). Physician review of EMED clinical records identified cases of post-injury laryngotracheal and esophageal procedures performed immediately after injury and documented subsequent injury management. The Military Health System Data Repository was queried for immediate post-injury acute care hospitalization and intensive care unit days. Descriptive data were collected on patient demographics, mechanism of injury, mortality, and theater of operation.

In an initial cohort review of 111 injured patients (109 battle injuries), battle injuries occurred through blast injuries or gunshot wounds. Approximately 53.2 percent of cases were penetrating neck traumas while 46.8 percent were inhalation injuries.

Of the penetrating neck trauma, 59 percent were dead on arrival. For airway management of non-fatal penetrating injuries, most patients (n = 21) were intubated orotracheally, of which 62 percent concluded the need for surgical intervention including vascular intervention, airway reapproximation, and pharyngoesophageal reapproximation. The few patients that were not intubated received an emergency cricothyroidotomy, endotracheal tube placement or an awake tracheostomy. A majority of inhalation injuries underwent bronchoscopy with an average initial bronchoscopy injury score of 2.2, indicating moderate injury. The burn surface area averaged around 38 percent including an average of two percent facial burns.

Review of the immediate post-injury period for the cohort revealed that acute care hospital length averaged 49.5 days while intensive care unit stay averaged 23.9 days.

These findings provide preliminary insight into the assortment of neck trauma treated among Service members and the sophistication and range of procedures needed to preserve life following injury.

This effort was supported with funding from the U.S. Navy Bureau of Medicine and Surgery's Wounded, Ill, and Injured Program.

Developing an Evidence Base to Refine the Decision-making and Clinical Management of Veterans and Service Members with Retained Embedded Metal Fragments from Blasts

Researchers at the University of Maryland (Baltimore, MD) are conducting a complementary set of animal and human studies to assess the health effects of blast injury and embedded metal fragments. These four unique projects address specific knowledge gaps that challenge the care of patients exposed to improvised explosive devices (IEDs) or other high kinetic energy weapons where embedded fragments were retained in the body. Specifically: (1) the Health Effects of Embedded Fragments of Military-Relevant Metals project examines the absorption and effects of embedded fragments in tissue. In this study, animals implanted with toxic metals commonly used in the battlefield were assessed weekly for multiple health variables. Preliminary findings show that some implanted metals have resulted in rapid tumor formation near the implantation site. (2) The Identification of Biomarkers for the Early Detection of Adverse Health Effects Resulting from Embedded Metal-Fragment Wounds project aims to identify early biomarkers of tissue injury that may signal the need for fragment removal. Skeletal muscle samples collected from animals implanted with metals at different timepoints after injury were analyzed for changes in gene activity. Early results show that tissue exposed to nickel and lead had different gene activity after one month of exposure; cobalt exposure resulted in changes in gene activity after three months. (3) The Biomarker Assessment of Kidney Injury from Metal Exposure in Toxic Embedded Fragment (TEF) Registry Veterans project aims to assess biomarkers of early kidney damage in Veterans registered in the VA TEF registry and injured with a fragment. (4) The Respiratory Health in a Cohort of TEF Registry Veterans Exposed to Blasts and Metals study aims to

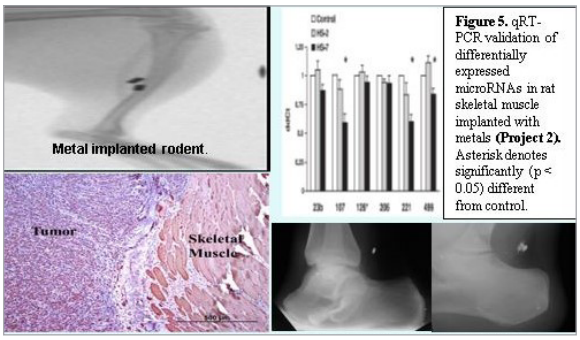


FIGURE 7-25: Top Left: Metal implantation in rodent, Bottom Left: Desmin-staining of tumor tissue following metal implantation in rodent Top Right: Validation of different microRNA activity in rat skeletal muscles implanted with metals compared to animals without implants. Asterisk denotes significantly ($p<0.05$) different from control. Bottom Right: X-ray of Veteran with embedded metal fragment deforming. (Figure used with permission from the authors)

examine lung function and insult from both metal inhalation and blast effects from the traumatic injury in this same VA-TEF Registry cohort (Figure 7-25). Participant recruitment and data collection for projects three and four are underway.

This effort is supported by the Peer Reviewed Medical Research Program (PRMRP) with strategic alignment to JPC-6 and JPC-7.

Two Independent Predictors of Nightmares in Posttraumatic Stress Disorder

Experiences of nightmares and disturbing dreams (NM/DD) are frequently reported symptoms of TBI and PTSD in U.S. military Veterans; however, due to their subjective nature, it is exceedingly difficult to document and/or quantify precisely. This leads to complications in assessing symptom severity and testing the efficacy of new or existing treatments for NM/DD. Researchers with the Veterans Administration (VA) and the Stanford University School of Medicine (Stanford, CA) used subjective morning reports along with mattress actigraphy in a U.S. military Veteran cohort over a longitudinal time frame to develop a predictive model of NM/DD endorsement.

The researchers recruited 31 male U.S. military Veterans currently enrolled as in-patients for treatment of PTSD. Participants received alerts seven times daily, pushed to mobile devices, to assess momentary mood and NM/DD reports, and slept on mattresses equipped with sensors measuring heart rate, respiratory sinus arrhythmia (RSA), sleep efficiency, and apnea-hypopnea index (AHI).

The researchers collected 468 morning reports, 60 percent of which indicated endorsement of NM/DD during the previous night. Multiple logistic regression models were computed with the behavioral and actigraphic parameters; only elevated AHI and low prior-night sleep RSA independently predicted morning NM/DD endorsement. These results confirm prior findings linking disturbed dreaming with sleep-disordered breathing and provide further autonomic correlates of NM/DD that may guide future treatment avenues.

This effort was managed by CDMRP with support and program oversight by MOMRP/JPC-5.

Surgical Tool Development

Load Transducer Engineering Solutions for Ultrasound and Surgical Tool Integration and a Functional Web-based Data Management and Querying System to Support Reference Models for Musculoskeletal Tissue Layers

Engineers at the Cleveland Clinic (Cleveland, OH) developed an instrumentation strategy to integrate a load transducer into any ultrasound system for freehand measurement of probe forces during imaging (*Schimmoeller et al., 2019*). An ultrasound system instrumented with a load transducer provides the capability to measure internal deformations of organs as a function of external loading. This tool helps quantify anatomical and mechanical variations of multi-layer tissues of musculoskeletal extremities, which are used for development of models for surgical simulations and can be leveraged to design protective gear for musculoskeletal extremities.

In demonstration of this functionality, an ultrasound system with an integrated load transducer was used to characterize the skin, fat, and muscle thickness of 100 human volunteers at multiple sites along the legs and arms (*Neumann et al., 2018*). Tissue thicknesses were measured under two conditions: unloaded (minimal force applied) and loaded (at a rate greater than 1 N/second). The data were used to create a database of anthropomorphic measurements, toward a broader goal of establishing a reference set of finite element representations of the non-linear mechanics for multi-layer tissue structures.

To organize and publicly disseminate the data, the researchers developed a web-based data management and querying system (https://multisbeta.stanford.edu/).

The instrumentation strategy designed for the ultrasound system has been extended to surgical tools to quantify forces of fundamental surgical acts (*Schimmoeller et al., 2018*). Ongoing experimentation and model development efforts, and additional data and models can be accessed through the public project site at https://simtk.org/projects/multis.

This effort was managed by CDMRP with support and program oversight by Medical Simulation and Information Systems/JPC-1.

Program Area: Reset

The DoD Blast Injury Research Program Coordinating Office is committed to reducing recovery time and improving the QOL for Service members who have experienced blast injuries. These efforts maximize the possibility of their RTD and reintegration into the civilian community and workforce. Medical research in the area of Reset informs evidence-based clinical guidelines for procedures that restore critical function and improve disfigurement. It also forms the basis for rehabilitation programs for blast-related psychological disorders, amputations, and other injuries with long-term effects on QOL. Reset strategies supported by extensive medical research enable the DoD and the military medical community to retain the confidence and trust of Service members, their Families, and the American public through measurable improvements to Service member recovery.

Chronic TBI Outcomes and Treatment Strategies

A Precision Medicine Approach to Chronic mTBI Leads to Improved Post-treatment Outcomes

The heterogeneity of TBI sequelae suggests that uniform therapies for subjects with chronic symptoms may not be broadly effective. In the absence of FDA-approved drug treatments, standardized clinical practice guidelines that can be implemented across a wide range of TBI symptoms are needed to treat chronic TBI. Researchers at the University of Pittsburgh (Pittsburgh, PA) developed a clinical trial protocol called "Targeted Evaluation, Action, and Monitoring of Traumatic Brain Injury (TEAM-TBI)." TEAM-TBI is a multi-modal approach of efficacious targeted therapies and technologies which can provide large-scale and cost-effective treatment for TBI. Subjects enrolled in the trial complete a comprehensive intake evaluation, including neuroimaging and biomarker assessments, to assess the clinical trajectories of TBI patients as well as the heterogeneity of the injury. Patients are stratified into clinical TBI trajectories, which include psychological health, sleep disruption, cognitive impairment, oculomotor disturbance, vestibular impairment, and post-traumatic headache (Figures 7-26 and 7-27). A multi-disciplinary clinical

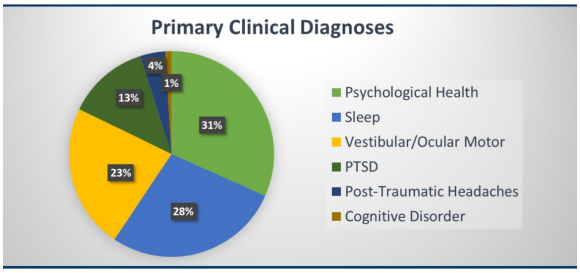


FIGURE 7-26: Breakdown of primary clinical diagnoses (n=88) that resulted from a multi-disciplinary adjudication process. A Psychological Health issue (*i.e.*, mood, anxiety), in isolation of PTSD, was the most common primary diagnosis. (Figure used with permission from the authors).

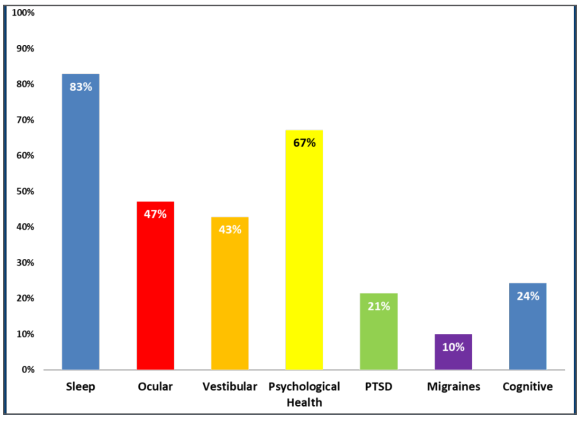


FIGURE 7-27: Percentage of TEAM-TBI participants with clinical diagnoses in each of the 7 domains (n=88). Each participant was adjudicated to have up to 5 diagnoses. Sleep was the most frequent finding amongst all participants. (Figure used with permission from the authors).

team establishes individualized treatment regimens tailored to address an individual's collection of TBI-related sequelae in a fully integrated manner. Participants receive a suite of interventions, including in-home therapies (physical and telemedicine) corresponding to a six-month targeted treatment. Interventions include activity and sleep monitoring, personal coaching, and mindfulness and cognitive training.

A six-month follow-up assessment is then conducted to compare the effectiveness of the individualized treatment regimen. Data published on early study completers show that patients demonstrated significant improvement from pre- to post-intervention on total symptoms, verbal memory, balance, vestibular/ocular, and cognitive outcomes (Figure 7-28). Early study results suggest that subjects with chronic symptoms that were unresponsive to therapy may benefit from targeted and individualized interventions.

The TEAM-TBI approach could provide a personalized medicine approach to TBI by guiding targeted therapies for improving cognitive function and decreasing symptoms.

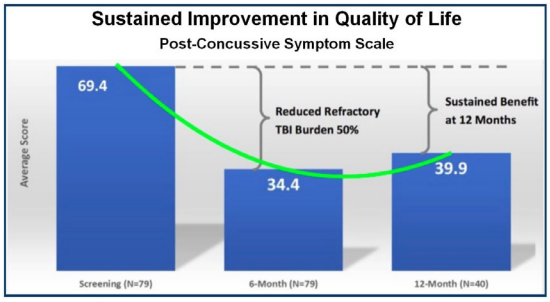


FIGURE 7-28: Symptom burden was calculated by self-report using the Post-Concussive Symptom Scale at screening (before enrollment; n=79), at the conclusion of the intervention (6 months after enrollment; n=79), and again 6 months after study completion (12 months from enrollment n=40). Symptom burden decreased on average by 50 percent after the treatment phase. This reduction in symptoms was sustained 6 months beyond study completion, indicating a durable improvement in QOL. (Figure used with permission from the authors).

This effort was managed by CDMRP with support from PH/TBIRP and programmatic oversight by CCCRP/JPC-6

The Chronic Effects of Neurotrauma Consortium (CENC) Characterizes Chronic TBI and Associated Comorbidities in Service Members and Veterans and Correlates Injury to Long Term Outcomes

The CENC is a joint Department of Defense (DoD) and Department of Veterans Affairs (VA) effort addressing the long-term consequences of mTBI in Service members and Veterans. The CENC is coordinated by researchers at Virginia Commonwealth University (Richmond, VA) and includes collaborators from 57 academic institutions, Veterans Affairs Medical Centers, and Military Treatment Facilities nationwide. The CENC seeks to understand the association (onset, prevalence, and severity) of the chronic effects of mTBI and comorbidities and probe for correlations to neurodegenerative disease.

Recently, CENC has published a synthesis of overarching clinical and cognitive findings from six of its major clinical research studies (*Cifu et al., 2018*). Collectively, these studies included 1,643 Service members and Veterans who served on active duty in Operation Enduring Freedom (OEF), Operation Iraqi Freedom (OIF), and/or Operation New Dawn (OND); 1,216 of these participants experienced at least one concussive event during their deployment. Clinical assessments including the Patient Health Questionnaire-9 (PHQ-9), Posttraumatic Stress Disorder Checklist (PCL-5), Pittsburgh Sleep Questionnaire Inventory, and several tests of cognitive dysfunction were used among the studies. Mean scores across studies for the PHQ-9 and PCL-5 indicated subclinical levels of psychological distress. Notably, participants reported a greater sleep onset latency and fewer hours of sleep per night than a clinical insomnia sample (*Backhaus et al., 2002*). Mean onset latency ranged 39.8–44.7 minutes in the CENC studies compared to 20.6 minutes in the

insomnia study, and mean sleep duration was approximately 5.4 hours in the CENC studies compared to 6.5 hours in the insomnia study. Cognitive evaluations indicated average working memory, processing speed, attention, and executive function.

Other important findings within individual CENC studies include: chronic balance disturbance among those who experienced repeated mTBI events (*Walker et al., 2018*); a significant association of mTBI with Veterans Affairs service-connected disability rating (*Dismuke-Greer et al., 2018*); increased opioid prescribing in Veterans with self-reported severe persistent post-concussive symptoms (*Bertenthal et al., 2018*); increased odds of sensory dysfunction among those with any TBI (*Swan et al., 2018*); reduced functional connectivity of the default mode network with increasing perception of pain among those with mTBI (*Newsome et al., 2018*); and greater levels of exosomal tau and p-tau in those with three or more mTBI than in those with two or fewer mTBI, with higher tau and p-tau levels significantly correlating with posttraumatic and post-concussive symptoms (*Kenney et al., 2018*).

This effort was managed by CDMRP with support from VA and PH/TBIRP (aligned to CCCRP/JPC-6 and CRMRP/JPC-8).

Chronic Effects of Neurotrauma Consortium (CENC) Studies Investigate the Potential Relationships Between TBI and Dementia

The CENC is coordinated by researchers at Virginia Commonwealth University (Richmond, VA) and includes collaborators from 57 academic institutions, Veterans Affairs Medical Centers, and Military Treatment Facilities nationwide. The CENC seeks to understand the association (onset, prevalence, and severity) of the chronic effects of mTBI and comorbidities and probe for correlations to neurodegenerative disease. One area of particular interest for the CENC is to investigate potential correlations between TBI and Parkinson's Disease or dementia. In FY18, CENC researchers published two papers examining these linkages.

Researchers at the San Francisco Veterans Affairs Medical Center and the University of California, San Francisco retrospectively examined records from a random sampling of patients with and without TBI, and without dementia at baseline, from Veterans Health Administration (VHA) databases (n = 325,870). They found that a history of TBI is associated with an increased risk of Parkinson's Disease (hazard ratios for mTBI: 1.56, all severity TBI: 1.71, moderate-severe TBI: 1.83) (*Gardner et al., 2018*).

This group also investigated associations between TBI severity, loss of consciousness, and dementia. Their study included 178,779 patients diagnosed with a TBI in the Veterans Health Administration health care system and 178,779 patients in a propensity-matched comparison group, none of whom had dementia at baseline. The prevalence of eventual dementia diagnosis was relatively low in both cohorts but was higher in those with TBI than in those without TBI (6.1 vs 2.6 percent). Adjusted hazard ratios for dementia were 2.36 for mTBI without LOC, 2.51 for mTBI with LOC, and 3.77 for moderate to severe TBI (*Barnes et al., 2018*). Characterization of the relationship between TBI and dementia-related diagnoses may lead to increased awareness of the risk of military service-connected TBI and dementia that may develop later in life.

This effort was managed by CDMRP with support from VA and PH/TBIRP (aligned to CCCRP/JPC-6 and CRMRP/JPC-8).

TBI Biomarkers

Plasma Metabolomics Biomarkers for Acute Mild Traumatic Brain Injury
Researchers at the University of California (Irvine, CA), the University of Rochester (Rochester, NY) and Georgetown University Medical Center (Washington, D.C.) conducted a study to identify biomarkers for TBI. Blood samples were collected from 62 college athletes, including 38 athletes diagnosed with at least one mild TBI (mTBI) within six hours of injury, and two, three, and seven days post-injury. Analysis of the blood plasma identified six metabolites that are present at different concentrations in athletes after injury compared to athletes without a TBI within the first six hours after injury and which continued to be present up to seven days postinjury (*Fiandaca et al., 2018*).

The six-metabolite panel was validated in a second cohort consisting of 84 individuals (31 with at least one TBI), including military personnel and sports injured individuals. This is the first panel of easily accessed, minimally invasive biomarkers of mTBI and would be readily adapted to a platform for field use. The replication in the military sub-cohort indicates that the panel could be, upon further validation, used as a preliminary adjunct for determination of withdrawing individuals from duty due to potential for impaired function.

This effort was supported by the Parkinson's Research Program.

Lysophosphatidic Acids Levels as Biomarkers of Blast-induced Traumatic Brain Injury
Levels of lysophosphatidic acids (LPAs), fatty acid derivatives reported to promote inflammation, have been shown to increase in the cerebrospinal fluid (CSF) of mice and humans after brain injury. To determine the potential of LPA levels as biomarkers for blast-induced traumatic brain injury (bTBI), investigators at the Walter Reed Army Institute of Research (WRAIR; Silver Spring, MD) in collaboration with University of Kentucky (Lexington, KY) are characterizing changes in LPA species in the CSF and plasma in animals after exposure to single and repeated blasts using an advanced blast simulator.

Preliminary studies have shown that several LPA species increase acutely in the CSF and plasma after single and repeated blasts. LPA levels correlated positively with the number of blasts. These findings demonstrate the potential of LPA levels to serve as acute biomarkers of blast injury in affected Service members.

This effort was supported by MOMRP/JPC-5.

Cerebrospinal Fluid Levels of Phosphorylated Neurofilament Heavy Chain Protein as a Chronic Biomarker of Blast-induced Traumatic Brain Injury
Neurofilament heavy chain (NFH) is a protein that supports neuron integrity and function. Phosphorylation of NFH (pNFH) affects its function and is known to be involved in neurodegeneration. Increased levels of pNFH in the cerebral spinal fluid (CSF) and plasma has been used as a biomarker of different neurodegenerative diseases. The researchers at Walter Reed Army Institute of Research (WRAIR; Silver Spring, MD) are evaluating the utility of pNFH as a chronic biomarker of blast-induced TBI in animal models using an advanced blast simulator. Preliminary findings indicate that pNFH levels increase significantly in the CSF at six months and one year after single and repeated blast exposures (Figures 7-29 and 7-30). These findings reveal the potential of CSF pNFH levels as a biomarker of blast injury progression in affected Service members.

This effort was supported by MOMRP/JPC-5.

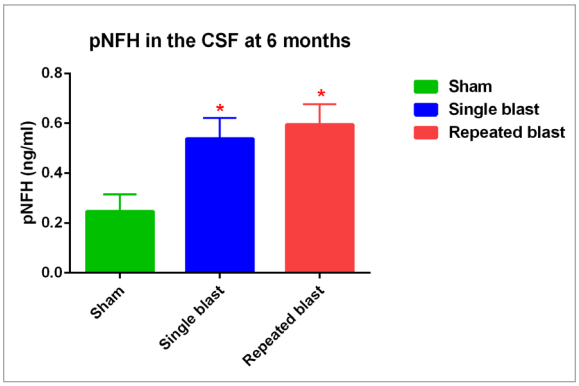


FIGURE 7-29: pNFH levels in the CSF at 6 months after single and repeated blast exposures. (Figure used with permission from the authors).

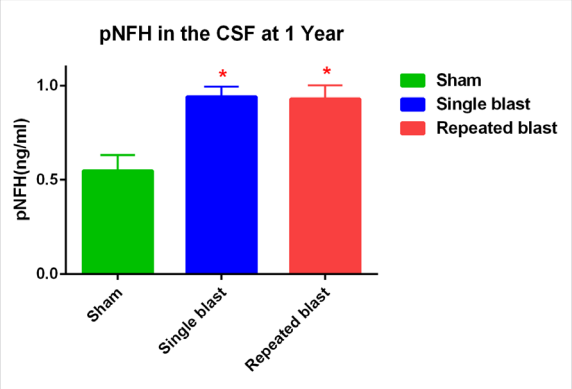


FIGURE 7-30: pNFH levels in the CSF at one year after single and repeated blast exposures. (Figure used with permission from the authors).

Structural Alterations to Neurons Following Stretch Injury In Vitro

There is evidence that different regions of the brain exhibit different material properties, potentially leading to varying tolerances to traumatic injuries such as TBI. One theory to explain this difference is regional differences in the ratio of different brain cell types, specifically neurons/glia (Figure 7-31). The influence of mechanical loading on the brain was assessed by systematically injuring a mixed culture of primary neurons and glia in culture with known loading conditions, and quantifying measures to evaluate structural alterations.

The study revealed that altering the ratio of neurons to glia changes the response of neurons following stretch injury (Figure 7-32; *DiLeonardi et al., 2018a*). To understand the injury mechanisms responsible for functional deficits, a link between the mechanics of brain injury and the functional consequences must be provided. Current work utilizes a new state-of-the-art mechanical stretcher (MEASSuRE). The MEASSuRE system delivers a tailorable load to cultured neurons while simultaneously recording cellular electrical activity and high-speed imaging. MEASSuRE allows, for the first time, the evaluation of changes in neuronal activity from the (1) control, undamaged state, to the (2) initial primary injury, and (3) through the downstream secondary injury cascades in one continuous data stream, with temporal resolution. Preliminary data verifies

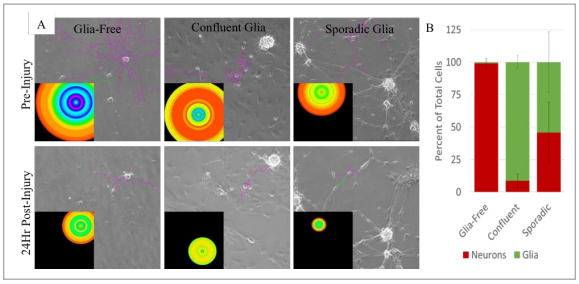


FIGURE 7-31: A) Pre- and Post-stretch images of cultures under different glia conditions. Neurites are traced to quantify number of branch points. Heat map rings show number of branch points as a function of distance from the cell body. B) Quantification of neuron to glia ratio based on different glia conditions. (Figure used with permission from the authors).

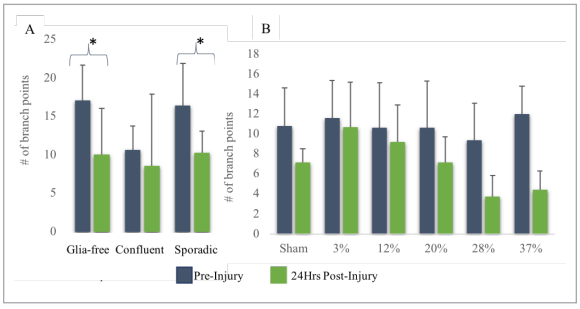


FIGURE 7-32: A) Quantification of neurite branching following stretch under different glia conditions. Significant decrease in amount of branching when no or sporadic glia present. No effect of injury on branching when glia form a complete uniform layer. B) Quantification of branching following different strains (3, 12, 20, 28, and 37 percent). Threshold for structural damage between 20 and 28 percent. (Figure used with permission from the authors).

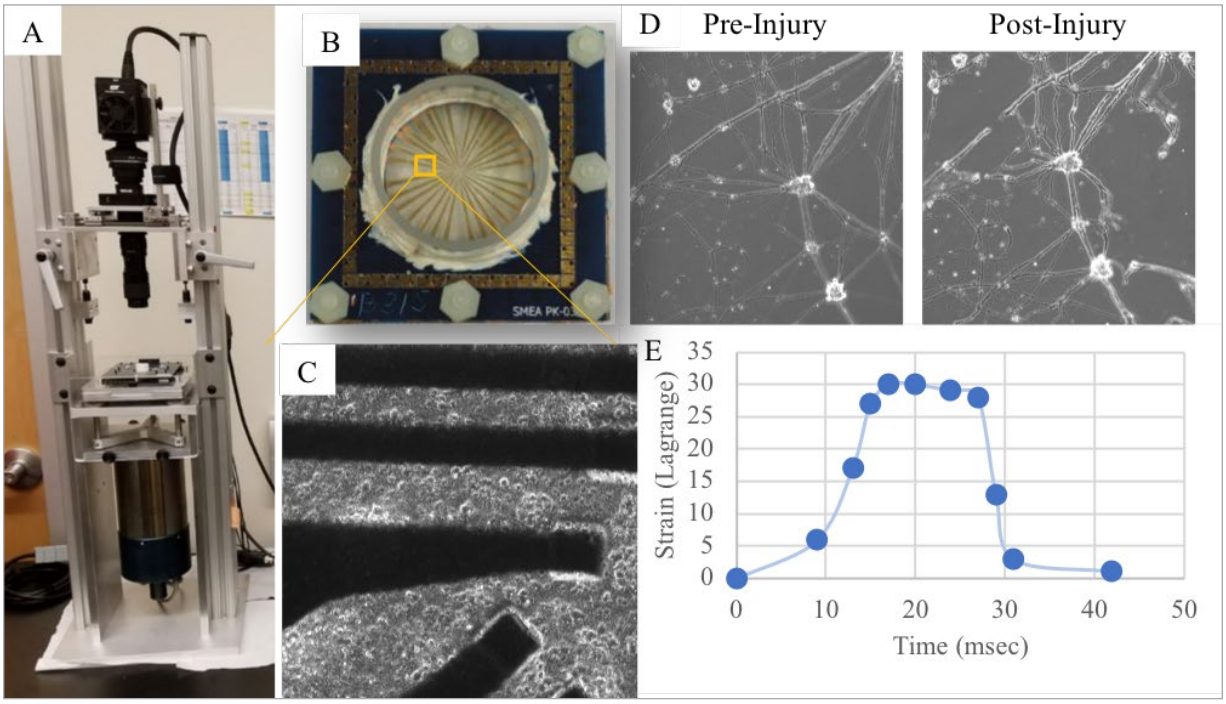


FIGURE 7-33: A) New MEASSuRE equipment. B) Example of a stretchable microelectrode array (sMEA). C) Example of neuronal culture grown on sMEA. D) Representative micrograph of culture pre- and post- 30 percent stretch. E) Strain history of neurons under 30 percent strain. (Figure used with permission from the authors).

a strain response measured directly from the neurons in culture during stretch injury (Figure 7-33; *DiLeonardi et al., 2018c*). Through this study, injury criteria can be established for use in classification of injury and to support computational models for the development and evaluation of future protective equipment.

This effort was supported by the ARL Basic Research Program.

Orthotics and Prosthetics

Intrepid Dynamic Exoskeletal Orthosis Use Produces Improvements in Pain and Walking Speed

The Intrepid Dynamic Exoskeletal Orthosis (IDEO) is a unique, custom-designed dynamic response device prescribed for patients with a wide variety of severe neuromusculoskeletal foot and ankle injuries. Researchers at the Center for the Intrepid at Brooke Army Medical Center (BAMC; San Antonio, TX) conducted a prospective study to quantify changes in pain and function when individuals with severe lower limb injury wear an IDEO compared to when they do not. It was hypothesized that the IDEO would (1) reduce walking pain, (2) increase walking speed, and (3) improve agility. Participants were assessed when they received their initial IDEO before they participated in any formal physical therapy with the device. Walking pain and physical performance (walking speed and agility) were evaluated.

Thirty-seven subjects completed testing. Subjects' injuries included fracture, nerve injury, osteoarthritis, Achilles tendon rupture, and compartment syndrome. On average, participants reported their pain to be 55 percent lower when walking with the IDEO as compared to walking without the IDEO. Average walking speed was 0.28 m/sec faster with the IDEO (1.30 ± 0.25 m/sec) than without the IDEO (1.14 ± 0.27 m/sec). Participants completed an agility assessment an average of 0.32 sec faster with the IDEO (8.19 ± 1.99 sec) as compared to without the IDEO (8.51 ±

2.42 sec). Improvements in pain and walking speed were immediate with the IDEO alone (without physical therapy). However, IDEO use without physical therapy did not significantly affect agility.

The IDEO provides several benefits to Service members with a wide variety of foot and ankle injuries. Understanding of the impact of the IDEO will help refine the IDEO prescription process for Service members with severe lower limb neuromusculoskeletal injuries.

This effort was supported by EACE.

Development of a Securely Adhered Prosthesis for Service Members Following Blast-related Limb Loss

Individuals with lower limb loss often complain about liner slippage and perspiration inside their prostheses when they are active in hot and humid environments or are engaged in vigorous activities. To address this problem, these individuals must remove their prosthesis and dry their residual limb to minimize prosthesis slippage and prevent complete loss of prosthetic adherence. Service members with lower limb loss need a prosthesis that remains securely adhered despite profuse perspiration. This research compared a novel, dynamic air exchange prosthesis designed to unobtrusively expel perspiration with a standard-of-care prosthesis.

Twelve transtibial amputees who were moderately active community ambulators were fit with a modified, patellar tendon bearing socket, and two study suspensions by a certified prosthetist. The study of prosthetic suspensions included: (1) a liner with a distal PIN lock (PIN; the standard method of care) and (2) a suspension with a pump that drives dynamic air exchange (DAE) using a sock worn between the liner and residuum that removes accumulated moisture. Subjects walked on a treadmill in 50 percent relative humidity at various temperatures (20, 30, and 35 degrees Celsius). Perspiration amounts were weighed, and prosthesis slippage was determined by measuring the distance between the location of the prosthesis originally and after walking (Figures 7-34 and 7-35).

FIGURE 7-34: Dynamic Air Exchange prosthesis with blue system harness worn by a subject while standing. (Figure used with permission from the authors).

FIGURE 7-35: Dynamic Air Exchange prosthesis with black system harness worn by a subject while standing. (Figure used with permission from the authors).

Prosthesis slippage was similar for both the PIN and DAE technology at 20 degrees Celsius, but the PIN slipped twice as much as the DAE at higher temperatures, suggesting the DAE may adhere better under more challenging circumstances. More moisture accumulated with the DAE compared to the PIN suspension at all temperatures. However, the DAE prosthesis removed up to 50 percent of the total perspiration depending on the temperature. These results suggest the DAE technology helps maintain mobility of active Service members with a lower limb amputation in a greater range of environments that require a securely adhered prosthesis.

This effort was supported by PRORP with strategic alignment to CRMRP/JPC-8.

Sensing and Actuation Systems for Monitoring and Adjusting the Comfort and Fitting of Prosthetic Socket

After amputation, fluctuations in limb volume throughout the day can affect the fit between the residual limb and a prosthetic socket. This can cause discomfort, skin irritation, and ulcers, and may lead to rejection of the prosthesis. To aid in maintenance of a proper fit, researchers at the University of Texas (Arlington, TX) designed a microstrip patch antenna sensor to simultaneously measure shear and pressure stresses at the limb-prosthesis interface (*Huang, et al., 2017*). The sensors were implanted in textile material (*e.g.*, denim) and embedded in prosthetic silicone liners, together called a "smart liner." A compact, portable sensor interrogation unit was developed to enable real-time data collection from the embedded sensors.

In addition, dynamic actuator inserts designed to monitor and modulate pressure at the limb-prosthesis interface were further developed (initial work described in *Carrigan et al., 2016*). The actuator inserts were integrated into an ankle-foot orthosis device worn by a healthy volunteer to test pressure mapping and modulation capabilities during walking. Upon positive results, both the custom-made liner and the dynamic actuators were integrated to a transtibial prosthesis and tested for feasibility and usability by an individual with transtibial amputation. Data analysis is ongoing, but if successful, the smart liner will enable monitoring of socket fit during daily activities and can be used to guide the adjustment of the dynamic actuator, leading to more comfortable prosthetic sockets.

This effort was supported by the PRORP with strategic alignment to CRMRP/JPC-8.

Development of an Impact Testing Standard for Prosthetic Feet

There is currently no accepted test standard for prosthetic feet to demonstrate durability to impact loading that may be encountered in physically demanding professions. To address this need, researchers from the Minneapolis Veterans Affairs (VA) Health Care System (Minneapolis, MN) built a system to pilot-test the impact resilience of a selection of prosthetic feet marketed for high-activity users (*Nickel et al., in press*).

Impact resilience was assessed for three sets of specimens each of nine prosthetic feet by determining their maximum drop height without failure. The test specimens (n = 27) were organized into three sets with different spring categories for particular user masses. Sets A, B, and C were tested with 45.9, 57.8, and 61.5 kg respectively (101, 127, and 135 lbf, respectively) simulating the mass of the user plus an added 22 kg (48 lbf) of worn or carried load and divided by two to represent even load distribution to both legs at impact.

The feet withstood drop heights without failure ranging from 20 to 100 cm. The type of prosthetic foot was found to significantly affect maximum drop height. Effect sizes for comparisons of individual feet range from 0.15

to 3.17 with the median effect size being 0.94, considered a large effect. In conclusion, the system successfully measures impact resilience and is sensitive to foot type. Large effect sizes indicate there are substantial differences between prosthetic feet marketed for active prosthesis users.

This effort is part of the BADER consortium and was supported by the PRORP with strategic alignment to CRMRP/JPC-8.

Customized 3D-Printed Prosthetic Devices for Wounded Warriors

Advanced prosthetic devices or adaptive attachments allow traumatically injured Service members with limb loss the ability to return to duty and participate in preferred recreational activities and sports. To meet this need, a multi-disciplinary team of clinicians and researchers at the DoD-VA Extremity Trauma and Amputation Center of Excellence (EACE; Fort Sam Houston, TX), and the 3D Medical Applications Center and Department of Rehabilitation at Walter Reed National Military Medical Center (WRNMMC; Bethesda, MD) used 3D printing in combination with computer aided design (CAD) software and 3D scanning technologies to develop custom orthotic and prosthetic devices for injured Service members with limb loss to improve functional capabilities (*Knight et al., 2018*). The devices are highly individualized, taking into consideration the individuals' preferences, activity needs, and abilities.

3D printing enables creation of devices from various materials such as plastic and titanium, allowing for greater tailoring of the device to the individual's needs. To date, over 200 Service members with limb loss have used these 3D-printed prosthetic devices and experienced an improved quality of life. This ongoing work provides a unique approach to develop customized devices for Wounded Warriors suffering from extremity trauma and limb loss and allows for the ability to participate in any and all desired activities.
This effort was supported by EACE and WRNMMC.

Knee Adduction Moment Peak and Impulse Do Not Change During the First Six Months of Walking with a Prosthesis

Individuals with unilateral lower limb loss are at increased risk for developing knee osteoarthritis in their contralateral limb. To better understand the mechanisms behind this outcome, researchers at the DoD/Veterans Administration (VA) Extremity Trauma and Amputation Center of Excellence (San Diego, CA) conducted a longitudinal assessment of knee joint kinetics during independent ambulation in individuals with lower limb loss (*Krupenevich et al., 2018*).

Gait analyses were conducted from Service members with lower limb loss (n = 8) as they walked at a self-selected speed and cadence. Data were collected zero, two, and six months after participants achieved independent ambulation. There were no significant differences between time points for the peak, loading rate, or impulse of knee adduction moment; peak knee flexion moment; or the peak or loading rate of vertical ground reaction force. In addition, although there was a significant time effect on stride length overall, there were no significant pairwise differences between time points. The results suggest that in individuals with lower limb loss, these aspects of contralateral knee joint kinetics do not change over the first six months of independently walking with a prosthesis.

This effort was supported by the CRSR, USU/EACE.

Running-specific Leg Prostheses

A multi-disciplinary collaborative team of researchers from the University of Colorado-Boulder (Boulder, CO), the Veterans Affairs (VA) Eastern Colorado Healthcare System, and VA Jewell Clinic Regional Amputation Center studied the effects of running specific prosthetic (RSP) model stiffness and heights on running and sprinting in Service members and Veterans with amputations. Participants in the study had unilateral (one side) or bilateral (both sides) transtibial (below the knee) amputations (TTAs). Their overall goal is to optimize the clinical prescription of RSPs, which

Photo credit: EJ Hersom/U.S. DoD

will ultimately maximize recovery, restore function, and improve and expedite orthopedic rehabilitation for people with amputations, while simultaneously saving time, money, and resources.

The researchers analyzed the biomechanical and metabolic effects of 30 people with TTAs (20 with unilateral and 10 with bilateral TTAs) using 15 different RSP configurations during running and sprinting. Each athlete used three RSP models (Össur, Freedom Innovations, and Ottobock) with three stiffness categories per model (manufacturer recommended, and ±1 stiffness category) at three different heights (prosthetist recommended, and ±2 cm). They determined the optimal configuration for running as the RSP that minimized metabolic demand while the optimal configuration for sprinting was the RSP that maximized speed.
Runners with unilateral and bilateral TTAs minimized metabolic cost during running by using the least stiff J-shaped Ottobock 1E90 Sprinter RSPs. For individuals with bilateral TTAs, stiffness reduction improved metabolic cost by 3.7 percent. Sprinters with unilateral and bilateral TTAs achieved faster maximum speeds by using the J-shaped Össur Cheetah Xtend and Ottobock 1E90 Sprinter RSPs and did so by increasing peak vertical ground reaction force and decreasing leg stiffness. Sprinters with bilateral amputations did so by decreasing ground contact time and increasing peak vertical ground reaction force.

These findings suggest that athletes with TTAs can best optimize distance-running and sprinting performance by using a specific RSP model and stiffness.

This effort is part of the BADER consortium and was supported by the PRORP with strategic alignment to CRMRP/JPC-8.

Extremity Injury Management

Low Back Pain in Persons with Lower Extremity Amputation: A Systematic Review of the Literature
Investigators at the Extremity Trauma and Amputation Center of Excellence (EACE; Tampa, FL) and the University of South Florida in Tampa, FL, performed a systematic review of the literature relating the presence and severity of lower back pain secondary to lower extremity amputation to determine the strength of evidence behind statements used to guide research and clinical practice (*Highsmith et al., 2018*). Eight empirical evidence-based statements were synthesized within the following categories: epidemiology, amputation level, function, disability, leg length, posture, spinal kinematics (mechanics), and osseointegrated (integrated into the bone) prostheses. Only the statements on epidemiology were moderately supported (by eight moderate quality studies). The four statements on

amputation level, leg length, posture, and spinal kinematics were supported by evidence at the low confidence level. The remaining three statements on function, disability, and osseointegrated prosthetic use were all supported by single studies or had comparable evidence that disagreed with study findings rendering insufficient evidence to support the statements.

Based on the state of the current evidence, appropriate preventative and treatment strategies to manage lower back pain in persons with lower extremity amputation remain a knowledge gap for future study.

This effort was supported by EACE.

Improving Functional Outcomes of Combat-injured Warfighters by Relieving Post-amputation Pain with Percutaneous Peripheral Nerve Stimulation

Peripheral nerve stimulation (PNS) is a promising non-opioid approach to pain management, but PNS systems have traditionally been limited by lead migration and the invasiveness of device implantation surgeries. A percutaneous PNS system was designed to reduce the risk of complications and enable delivery of stimulation without surgery. The therapy involves the percutaneous insertion of a fine-wire, coiled lead through an introducer needle to target one or more peripheral nerves with stimulation for up to 60 days, followed by removal of the leads (Figures 7-36 and 7-37).

Researchers from SPR Therapeutics (Cleveland, OH; a portfolio company of NDI Medical, LLC) conducted a multicenter, randomized, placebo-controlled trial designed to collect data on the use of their percutaneous PNS therapy for improving functional outcomes by alleviating pain in individuals with major lower limb amputations. The study included 28 patients with chronic pain following traumatic lower limb amputation. The PNS therapy successfully produced clinically

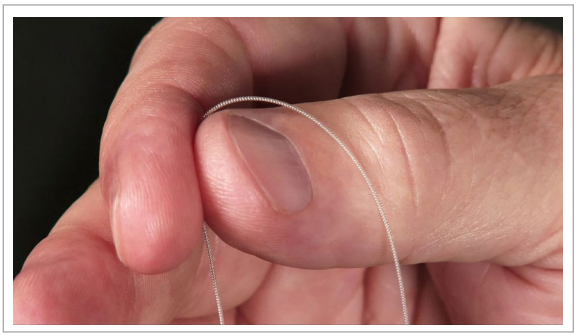


FIGURE 7-36: The novel percutaneous peripheral nerve stimulation system utilizes fine-wire coiled leads that are placed using an introducer needle, typically under ultrasound guidance. (Figure used with permission from the authors)

FIGURE 7-37: Fine-wire coiled peripheral nerve stimulation leads were placed percutaneously and connected to external, body-mounted stimulators. The stimulator is shown in place to treat post-amputation pain of the lower extremity. (Figure used with permission from the authors)

significant (at least 50 percent) and statistically significant reductions in post-amputation pain in most patients. Follow-up is ongoing; among patients that have completed a one-year follow-up, 10 additional months after the 60-day therapy period, a majority of patients continued to report at least 50 percent pain relief. Participants also reported less opioid usage and major reductions in pain interference—a key measure of function and disability associated with pain. These findings provide support for the use of percutaneous PNS for the treatment of chronic post-amputation pain following blast injury. This study demonstrates that percutaneous PNS can effectively treat pain in severely injured military Service members with amputations and

may enable them to improve their quality of life, accelerate rehabilitation, and resume active duty activities.

This effort was supported by the PRORP with strategic alignment to CCCRP/JPC-6 and CRMRP/JPC-8.

Targeted Muscle Reinnervation Shown to Reduce Amputee Pain and Phantom Limb Pain

Targeted Muscle Reinnervation (TMR) is an innovative surgery originally developed to enhance the use of advanced prosthetics. Researchers at Northwestern Memorial Hospital (Chicago, IL), Walter Reed National Military Medical Center (Bethesda, MD), The Ohio State University (Columbus, OH), University of Oklahoma Health Sciences Center (Oklahoma City, OK), and San Antonio Military Medical Center (San Antonio, TX) investigated the therapeutic effectiveness of TMR to reduce amputee limb pain and phantom discomfort (*Dumanian et al., 2018*). In a randomized clinical trial, 28 individuals with chronic major limb amputation pain received TMR or standard treatment. TMR treatment resulted in a significantly greater reduction in phantom limb pain and trended toward improved residual limb pain, compared to standard treatment for nerve and pain issues. The results were similar for patients with all mechanisms for limb loss, including blast injuries. As an adjunct to this clinical trial for the treatment of post-amputation pain, the successful prevention of amputee pain and phantom limb pain by using the TMR surgical technique during the initial amputation was also documented. TMR performed at the time of amputation was three times more likely to decrease pain and phantom severity compared to standard amputations.

This study raises awareness of TMR in the surgical community for the prevention of amputee pain and phantoms at the time of amputation and for treatment of established pain. The findings underscore the procedure's potential to revolutionize treatment and become the new standard of care for millions of individuals with amputations worldwide suffering from debilitating chronic pain.

This effort was supported by PRORP with strategic alignment to CRMRP/JPC-8.

Assessing Initial Treatment and Outcomes After Deployment-related Upper Extremity Injuries

The Naval Health Research Center (NHRC; San Diego, CA) conducted multiple studies exploring the outcomes of deployment-related upper extremity injuries. Extremity injuries account for a large percentage of combat injuries sustained in the most recent conflicts in Iraq and Afghanistan with amputation being the most serious extremity injury. Little research has focused on upper extremity (UE) amputation and subsequent treatment. Using the NHRC Expeditionary Medical Encounter Database (EMED), 55 individuals were identified with above elbow (AE) amputations and 93 with below elbow (BE) amputations. During the early phases of rehabilitation, the BE group received more manual therapy (*i.e.*, massage) and modalities (*i.e.*, ice) than the AE group. In the later stages of rehabilitation, the AE group received more occupational therapy (OT) treatment overall, especially more active treatments (*i.e.*, therapeutic exercise). Identifying OT intervention strategies and the timing of visits can provide critical information on clinical resource requirements and improve outcomes for patients with upper limb amputations (Figures 7-38 and 7-39).

Although the implications of acute injuries on delayed amputation in the lower extremity has been well-studied, little is known about the impact of these injuries on delayed UE amputation. In a second study, the investigators examining 2,679 Service members with UE injuries, delayed amputation was identified in 35

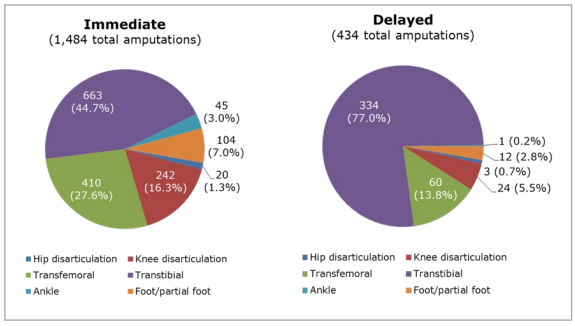


FIGURE 7-38: Lower extremity (LE) amputation location, by timing. (Figure used with permission from the authors).

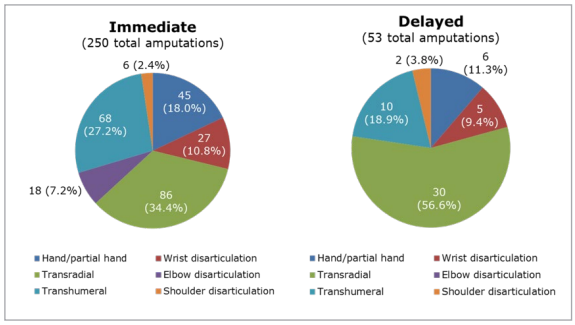


FIGURE 7-39: Upper extremity (UE) amputation location, by timing. (Figure used with permission from the authors).

(1.3 percent) injured Service members. The most common injury sites in this cohort of Service members with UE injuries were open fractures of the ulna, hand, and humerus. Yet, vessel and nerve injuries, as well as thumb amputations, were more likely to result in a delayed amputation. The odds of delayed amputation increased substantially when more than one of these injuries was sustained. Understanding the relationship between specific acute injuries and delayed amputation may guide clinical decision-making in the acute care period.

This effort was supported by EACE.

Comparing Immediate and Delayed Deployment-related Amputations

Extremity injuries comprise the largest proportion of injuries resulting from the conflicts in Iraq and Afghanistan. While advancements in medical care and technology have made limb salvage efforts possible, many extremity injuries still progress to amputation, either immediately (within the first 24 hours) or later as a result of failed limb salvage. To further explore amputation timing and why some extremity injuries proceed to delayed amputations and others do not, researchers at the Naval Health Research Center (NHRC; San Diego, CA) queried the Expeditionary Medical Encounter Database (EMED), a repository for deployment-related medical encounter information, for all major amputations (those of partial hand or foot and greater) from 2001 to 2017. Descriptive statistics were calculated to assess differences in characteristics between Service members with immediate or delayed amputations.

A total of 1,705 Service members with deployment-related amputations were identified from 2001 to 2017. Nearly three-quarters of this population sustained at least one immediate amputation (n = 1,241), while the remaining 464 (27 percent) sustained only delayed amputations. The groups differed in relation to the mechanism of injury, with 94 percent of the immediate group being injured by blast mechanism compared with 80 percent of the delayed group (p <.001). Gunshot wounds were more common in Service members with delayed amputations, at 11 percent compared to two percent of the immediate group (p < .001). The percentage of Service members injured in a non-battle injury was also twice as high in the delayed group, at six percent compared to three percent (p < .005). Groups also differed in regard to posture. Forty-four percent of individuals who underwent an immediate amputation were mounted in a vehicle at the time of injury compared to 62 percent of individuals with only delayed amputations (p < .001). In addition, those with an immediate amputation had a significantly higher mean injury severity score (ISS) than the delayed group (20.1 vs. 14.6, p < .001). Differences in amputation sites were also observed between the groups. Transtibial amputations were the most common lower extremity amputation site, accounting for 77 percent of delayed lower extremity amputations compared with only 45 percent of immediate lower extremity amputations. In the

upper extremities, transradial amputations were the most common in both groups, representing 57 percent of delayed upper extremity amputations but only 34 percent of immediate upper extremity amputations.

Using these findings, appropriate care and sufficient support for injured Service members can be planned and delivered to address their current and future needs.

This effort was supported by EACE.

Comparison of Functional Status Between Service Members After Deployment-related Amputations and Severe Lower Limb Injuries

Investigators at the Naval Health Research Center (NHRC; San Diego, CA) conducted a study to determine the long-term functional limitations associated with extremity injuries. The study collected and analyzed data from the Wounded Warrior Recovery Project (WWRP), a longitudinal study of Service members with deployment-related injuries. WWRP participants indicating use of a lower limb orthosis or prosthesis rated their ability to complete 20 activities on the Orthotics and Prosthetics Users' Survey (OPUS), thus providing a measure of functional status. The functional status among participants with either, (1) a deployment-related lower limb amputation who reported the use of a prosthesis (n = 82), or (2) a deployment-related severe lower limb injury who reported the use of an orthosis (n = 68) was compared. Overall, self-reported functional status was compared between the two injury groups by examining the total OPUS score and comparing the responses on the individual OPUS items.

Of the 82 participants with a lower limb amputation, 70 percent had a below knee amputation, while 30 percent had an above knee amputation. Of the 68 participants with a severe lower limb injury, 60 percent reported using an ankle orthosis, while others reported using a foot or knee orthosis. Proportions of acute fractures of the severe lower limb injury group were tibia (56 percent), fibula (43 percent), calcaneus (20 percent), and metatarsal (22 percent). When examining data on individual survey items, the item "getting into or out of tub or shower" was significantly more difficult in participants with an amputation and the item "put on or take off orthotic or prosthetic" was significantly more difficult in participants with a severe lower limb injury. The most difficult items reported by both groups were "walk up to two hours", "run one block" and "walk up a steep ramp" while the least difficult items were "getting on and off a toilet", "walking around indoors" and "carry a plate of food while walking."

These findings demonstrate that both groups of injured Service members are at risk for long-term secondary effects of these injuries, and rehabilitation efforts should be optimized to address specific areas of functional limitation.

This effort was supported by EACE.

Associations Between Trunk Postural Control in Walking and Unstable Sitting

Targeted training of trunk postural control (TPC) via isolated trunk control tasks may improve performance in activities like walking. To explore this relationship, researchers at the DoD/Department of Veterans Affairs (VA) Extremity Trauma and Amputation Center of Excellence (EACE) investigated TPC responses to perturbations during walking and sitting at multiple levels of demand (*Acasio et al., 2018*).

Participants with no recent history of illness, injury, or musculoskeletal disorders were included in the study (n = 13). The test conditions included walking on a treadmill at speeds ranging 20 percent above and below a self-selected walking speed and sitting in an unstable chair at 100, 75, 60, and 45 percent of each participant's neutral stability.

Local TPC (*i.e.,* resistance to continuous perturbations) was characterized through triplanar Lyapunov exponents and sample entropy. Global TPC (*i.e.,* response to finite perturbations) was measured by ranges of motion and, for seated trials, metrics derived from center-of-pressure time series.

There were no significant correlations between local TPC and the difficulty of test conditions during either walking or unstable sitting tasks. In contrast, global TPC declined with increasing task demand for both walking and unstable sitting, and there was a moderate inter-task relationship. This suggests global TPC may be similarly regulated in walking and sitting tasks, which supports the theory that improving TPC in one activity may translate to improvements in TPC during other.

This effort was supported by PRORP with strategic alignment to CRMRP/JPC-8.

Transplants and Grafts

3D Bioprinting of Customizable Bioactive Scaffolds for Repair of Long Bone Injury
Damage to the upper and/or lower extremities are becoming increasingly common among the injuries sustained by Service members. Treatment of these wounds requires complex reconstructive procedures and the need to replace damaged or lost bone.

A team of scientists at New York University School of Medicine (New York, NY) investigated an alternative strategy for the repair of long bone injuries. The investigators have developed a 3D-printed scaffold made of a calcium- and phosphorus-based ceramic material. When evaluated in a rabbit model of full thickness bone segmental defects (a cavity in the bone that cannot be filled without treatment), the implanted scaffold showed increased bone formation and remodeling along the scaffold, while defects not repaired with the scaffold showed limited healing at eight weeks. The scaffold was also shown to decrease in volume over time. This work demonstrates the ability of the developed scaffold to directionally regenerate and remodel bone, and potentially treat critical segmental bone defects for which there is currently no effective patient-specific treatment.

This effort was supported by the Reconstructive Transplant Research Program (RTRP) with strategic alignment to CRMRP/JPC-8.

Development of Synthetic Vascular Grafts
Battlefield wounds often involve vascular tissue damage requiring surgical interventions such as arterial repairs and vein bypass grafts. Synthetic vascular grafts are used routinely. However, challenges remain in the application of these grafts for small diameter vessels, as those currently available may result in complications such as obstruction, clot formation, and arterial wall thickening.

To overcome these obstacles, investigators from the University of Florida (Gainesville, FL) developed biodegradable tissue-engineered vascular grafts that more closely mimic the architecture of the native vessel. To this end, the team has created a bilayer scaffold consisting of a hollow polymeric tube surrounded by a thick layer of microscopic fibers containing essential vessel wall components collagen and elastin (*Goins et al., 2018*). The addition of these proteins to the construct will support the growth of vascular cell types to promote vascular integration and tissue regeneration.

Mechanical testing of the designed scaffold revealed that the scaffold closely matched the mechanical properties of native arteries. The grafts also supported adhesion and growth of blood vessel lining and muscle cells. Additionally, the scaffold could withstand physiologically relevant stresses and pressures.

Taken together, the promising characteristics of these newly developed synthetic vascular grafts have the potential to promote tissue regeneration for the repair and replacement of small diameter blood vessels.

This effort was managed by CDMRP with support and program oversight by CRMRP/JPC-8.

The Identification of Matrix Metalloproteinase 3 as a Potential Diagnostic Marker Discriminating Non-severe from Severe Rejection in Face Transplantation

Vascularized composite allotransplantation (VCA) is a reconstructive strategy that offers severely injured Service members improved tissue function and aesthetic appearance compared to conventional reconstructive surgery. VCA involves the transplantation of multiple tissue types, such as a hand/limb or face, as a functional tissue graft to replace and repair irreparably damaged tissues. While VCA has been successful, numerous challenges remain preventing its widespread use. These include the necessity for long term immunosuppression that can lead to serious negative side effects and a high rate of acute rejection. Identification of non-invasive biomarkers for monitoring rejection episodes following VCA will improve the ability to diagnose and treat rejection in a timely fashion to improve VCA recipient outcomes.

Investigators from Brigham and Women's Hospital (Boston, MA) determined if non-invasive blood biomarkers can be identified to detect rejection earlier. Serum samples were collected from six VCA recipients that experienced no-rejection, non-severe rejection, and severe rejection. Protein expression profiling was conducted on all samples and over 1,000 proteins were analyzed. Using computational analysis, a signature of five proteins was able to discriminate severe rejection from both no- and non-severe rejection samples. Of the five proteins identified, the enhanced expression of matrix metalloproteinase 3 (MMP3) during episodes of rejection, was technically validated using a second method, confirming the utility of this protein as a diagnostic marker for the discrimination of rejection episodes. These promising results will require further evaluation using a larger independent patient cohort. The identification of novel biomarkers to predict and diagnose rejection earlier will allow for timelier clinical intervention, greater personalization of post-transplant care, and improved outcomes for VCA recipients.

This effort was supported by RTRP with strategic alignment to CRMRP/JPC-8.

Promoting Long-term Graft Survival in Composite Tissue Allotransplantation

Composite tissue allotransplantation (CTA) another term for vascularized composite allotransplantation, is the transplantation of multiple tissue types as a functional unit, such as a hand/limb, face, or abdominal wall. One of the major hurdles to widespread use of CTA for severe injuries is the need for prolonged immunosuppression to prevent graft rejection. Extended immunosuppression can lead to many negative side effects including kidney or liver failure. Alternative strategies to suppress immune rejection would reduce prolonged immunosuppression and improve outcomes following CTA.

To this end, investigators at the University of Pittsburgh (Pittsburgh, PA) and Wake Forest Institute for Regenerative Medicine (Winston-Salem, NC) developed a controlled release drug delivery system consisting of microparticles (MPs) that slowly release agents involved in the recruitment (Recruitment-MPs) or expansion (Expansion-MPs) of regulatory T cells (Tregs). Tregs down regulate local immune responses but are found in relatively low numbers throughout the body.

By engineering MPs which release the Treg-attracting protein, CCL22, Tregs can be recruited to the transplanted allograft site to suppress

graft rejection. The Recruitment-MPs have been found to prolong graft survival over 200 days when administered in a rodent model of hind limb transplantation; untreated graft recipients rejected the implanted tissue within 2-3 weeks after immunosuppression cessation.

Additionally, the investigators developed Expansion-MPs, which release factors known to promote naive T cell maturation into Treg. When administered in a rodent hind limb transplant model, Expansion-MPs releasing the proteins IL-2 and TGF-beta, and the drug rapamycin, were shown to delay rejection more than 300 days (Figure 7-40).

Treatment with both Expansion-MPs and Recruitment-MPs led to decreased inflammation, increased numbers of Tregs in the lymph nodes, and Tregs with superior donor specific suppression of T effector cells compared to controls.

Minimizing the use of harsh immunosuppressive agents through the use of Recruitment- and Expansion-MPs will help enable the widespread use of CTA for severely injured Service members while enhancing quality of life and improving health outcomes for CTA recipients.

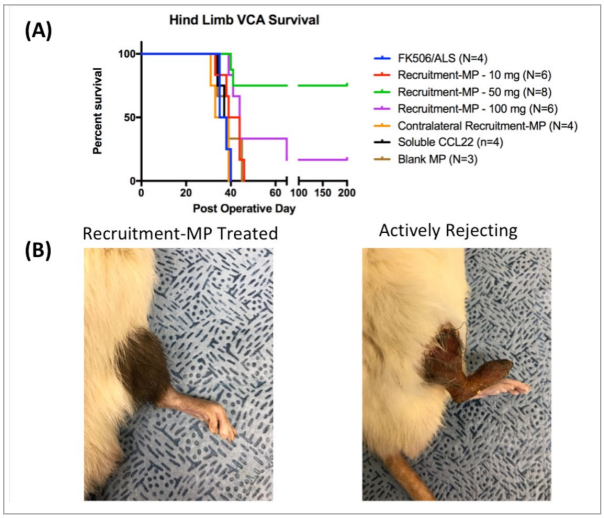


FIGURE 7-40: A) Treatment with 50mg of Recruitment-MP is able to prolong allograft survival to at least 200 days in 6/8 animals. This result is statistically significant $p<0.05$ when compared to all controls. B) Animals receiving a hind limb transplant were monitored daily and scored on a five-point rejection scale. Limbs displaying a progressive stage 3 rejection were considered "rejected." (Figure used with permission from the authors).

This effort was supported by RTRP with strategic alignment to CRMRP/JPC-8.

Acute Management/Surgery

Early Decompression Surgery and Patient Outcomes Following Cervical Traumatic Spinal Cord Injury

Researchers at the Hôpital du Sacré-Coeur de Montréal (Montreal, Canada) investigated the impact of early decompression surgery on neurological recovery and quality of life for patients sustaining cervical traumatic spinal cord injury (TSCI). In one study, 42 patients who sustained a motor-complete, cervical TSCI were followed for six months. Neurological recovery was assessed using the American Spinal Injury Association impairment scale (AIS) and neurological level of injury.

Analysis of the data revealed that neurological recovery of patients sustaining cervical TSCI can be improved by early decompression surgery performed within 19 hours post injury. Upon follow-up six months post injury, patients who received early decompression surgery showed more pronounced neurological improvement as assessed from the AIS. 75 percent of patients that received early decompression surgery improved at least one AIS grade versus 41 percent for those who did not.

Furthermore, the initial severity of the neurological injury after a cervical TSCI may be used to estimate quality of life (QOL) following injury. In a related study, the investigators assessed QOL of 119 individuals who sustained a cervical TSCI six to twelve months after injury. Those individuals who sustained less severe neurological injury scored more favorably on the self-reported SF-36 Health Survey, a QOL assessment tool. Additionally, this project also reports that despite

severe physical impairment, individuals with complete tetraplegia may report good mental QOL.

These findings are important to help clinicians define management strategies for patients, determine realistic expectations for recovery and quality of life, and optimize treatment plans based on the initial evaluation after a TSCI.

This effort was supported by SCIRP and strategically aligned to CCCRP/JPC-6 and CRMRP/JPC-8.

The PROOVIT Registry Provides a Contemporary Picture of the Management of Vascular Injury

The PROspective Observational Vascular Injury Trial (PROOVIT) is a prospective, multi-center observational trial on the management of vascular trauma and is a sub-study of the larger National Coordinating Center for Trauma Research study. A recent review of the registry investigated the incidence of arterial injuries and hospital resource use for open surgical and endovascular management of these injuries (*Faulconer, Branco, Loja, et al., 2018*).

Data from patients with arterial injury not distal to the knee or elbow were included in the study (n = 1,143 patients from 22 Level I trauma centers). Of these injuries, 456 were in non-compressible regions. The majority of those injuries were from blunt trauma (n = 356, representing 64 percent of reviewed blunt injuries), and were primarily managed conservatively (46.1 percent) or through endovascular surgery (40.2 percent). In managing transection and partial transection injuries to non-compressible regions (n = 97 endovascular and 77 open surgery), endovascular surgery required significantly fewer packed red blood cell units and had significantly higher in-hospital survival rates than open surgery. However, endovascular therapy required significantly longer hospital stays than open surgery. As demonstrated through this study, the PROOVIT registry can provide information required to answer questions about optimal diagnosis and management of patients with vascular trauma, including much needed long-term outcome data.

This effort was managed by CDMRP and supported by the Trauma Clinical Research Repository Program with programmatic oversight from CCCRP/JPC-6.

Simulations

A Novel Assessment for Readiness Evaluation during Simulated Dismounted Operations: A Reliability Study

The Center for the Intrepid (San Antonio, TX) developed a Readiness Evaluation during simulated Dismounted Operation (REDOp) assessment, performed in a virtual reality environment. This assessment consists of a simulated combat patrol with activities aligned with current doctrine and informed by input from previously deployed Service members. Measures of activity tolerance and shooting performance are used to identify limitations that may negatively impact a Service member's ability to successfully return to their occupation. The purpose of this investigation was to establish the psychometric properties of the novel REDOp assessment (Figure 7-41).

Eighteen able-bodied individuals with no history of musculoskeletal or neurologic injury participated in this study. They wore a Kevlar vest and helmet and employed a replicated M4 rifle during a simulated combat patrol performed in a virtual reality environment with a six degree-of-freedom motion platform with embedded treadmill. These individuals walked over variable terrain (*e.g.*, pitches and rolls of the platform) on the treadmill as speed and incline progressively increased over approximately 55 minutes, for a total distance

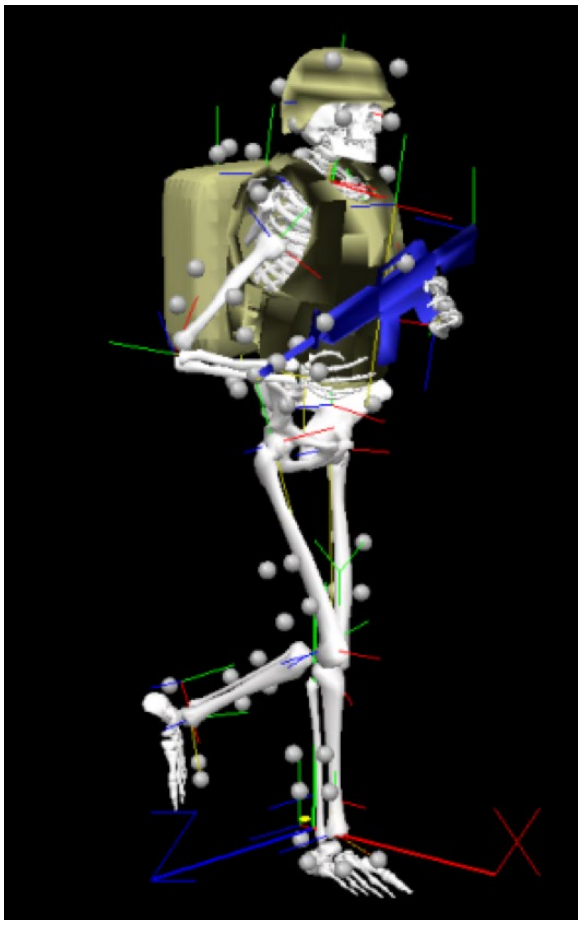


FIGURE 7-41: Three-dimensional biomechanical depiction of a subject participating in the Readiness Evaluation during Simulated Dismounted Operations assessment. The image was created from motion capture recordings while the participant wore body armor and carried a simulated weapon. White balls represent that tracking markers on each body segment and object. The color lines show the axes of these segments and objects. (Figure used with permission from the authors)

of 4.5 km. Participants progressed through the assessment until they requested to stop, were stopped by a member of the study team for safety concerns, or they completed the assessment. At specific intervals, 20 targets (10 enemies and 10 friendlies), would appear along the patrol. Participants had to identify all targets and make shoot/don't shoot determinations for each (shooting the enemy targets and avoiding the friendly targets) while continuing to walk. Each participant returned approximately two weeks later to repeat the REDOp assessment.

Distance traveled and shooting measures including accuracy, precision, and target acquisition time were similar between the two assessments. Out of the 18 participants, two completed all 4.5 km of the assessment in Session 1 and 6 completed it in Session 2. In Session 1, the primary performance limiter was cardiovascular endurance with 50 percent (9/18) of participants noting it as the reason for stopping. Pain was the next most common limiter at 28 percent (5/18) and 11 percent (2/18) stopped due to some combination of both cardiovascular endurance and pain.

REDOp's simulated combat patrol task has high ecologic validity and aligns with military occupational requirements.

This effort was supported by the Defense Health Program, the Center for Rehabilitation Sciences Research, Department of Rehabilitation Medicine, Uniformed Services University.

Developing a High-fidelity, Veteran-centric, Driving Simulator to Promote Road Safety

Motor vehicle crashes are a leading cause of injury and death for Veterans of our recent wars. Veterans are 75 percent more likely to die in a motor vehicle crash than the overall population (*Lew et al., 2011*). Effective driving interventions have potential to increase safety and reduce motor vehicle crashes and the resulting injuries and deaths. Furthermore, promoting driving fitness may also have carryover effects supporting other key arenas of community re-integration such as family function, employment, participation in society, and satisfaction with life. To this end, researchers at the University of Florida (Gainesville, FL) developed the "DriveSafety" high-fidelity simulator, based on the control panel from a Ford Focus and engineered into the cab of a passenger van. Veterans train with the DriveSafety simulator by driving the car through predesigned courses, during which their responses are monitored and assessed by a trained evaluator; past investigation by the group has shown the

need to train evaluators for consistency across tests. The scenarios are particularly Veteran-centric because they include items like roadside clutter, which presents a significant threat in battle environments where it can conceal improvised explosive devices (IEDs) but is a mere distraction in everyday driving. The Veteran is re-tested, ultimately narrating his experience to detail the use of techniques and practices learned from the evaluator, and driving improvements are recorded.

The University of Florida investigators have been engaged in a randomized controlled trial to show the ability of the intervention to reduce driving errors in the simulator. This study has demonstrated the feasibility of a protocol for use of the DriveSafety simulator as a rehabilitation tool for Veterans experiencing driving difficulty. Several disciplines, including psychology, social work, and community service coordinators that engage in the reintegration of Veterans, benefit as this work complements work they are engaged with to address driving difficulty, unintentional injury, and prevention. Development of this Veteran-centric content now makes it available to multiple military and Veterans Affairs (VA) websites using the DriveSafety simulators for rehabilitation (Figure 7-42). In addition to articles and a book chapter, the driving intervention has been presented at national conferences including those devoted to driving rehabilitation. By reducing driving errors, it is expected that Veterans will have a greater level of safety, and a reduced burden of crashes, unintentional injury, and other negative sequelae, thus enabling them to be more mobile within their communities.

This effort was supported by MSIS/JPC-1.

Neurophysiological Response to Blast

Characterization of Blast Exposure in a Large Sample of Military Personnel in Combat and Noncombat Environments

Researchers from the Naval Health Research Center (NHRC; San Diego, CA) are studying the effects of blast exposure on Service members involved in explosive ordnance disposal (EOD). Electrodermal activity (EDA), a proxy for sympathetic nervous system activity, was

FIGURE 7-42: DriveSafety Simulator (Figure used with permission from the authors).

monitored during periods of exercise in a group of EOD operators (n = 36). Dose-dependent effects in EDA were observed, such that those who endorsed blast exposure showed blunted EDA responses. Similar differences in EDA patterns were observed between those who reported combat exposure and those who did not. These associations were robust to numerous confounding influences. These findings suggest that blast and combat exposure disrupt sympathetic nervous system function under conditions of acute exercise stress. This may have downstream effects on cardiovascular and behavioral health.

This effort was supported by MOMRP/JPC-5.

Psychological and Quality of Life Outcomes

An Evaluation of Gender Differences in Postconcussion Symptoms and Mid-term Quality of Life Following Combat-related Traumatic Brain Injury

Investigators at the Naval Health Research Center (NHRC; San Diego, CA) examined differences in post-concussion syndrome (PCS) symptoms and quality of life (QOL) between men and women in combat following traumatic brain injury (TBI). To this end, the Expeditionary Medical Encounter Database (EMED), a clinical data repository containing point-of-injury information on all casualties sustained between 2001 and 2016 during military deployment, was queried for Service members with provider-diagnosed TBI sustained in Iraq. Service members also had to have enrolled in the NHRC's Wounded Warrior Recovery Program, an ongoing cohort study incorporating an online survey assessment evaluating QOL for military casualties. Symptoms of PCS were abstracted from electronic medical databases within one-year post-injury and included five categories previously identified by the Defense Veterans Brain Injury Center (DVBIC): psychiatric, neurologic, vision, sleep, and auditory.

A total of 1,414 men and 82 women were included in the study. The only PCS symptoms that significantly differed by gender were auditory symptoms, with higher rates in men (26 percent vs. 12 percent, p = 0.02). In gender-specific analyses, men with at least one PCS symptom had significantly lower QOL scores than those with no symptoms, as did women reporting two or more PCS symptoms (Figure 7-43).

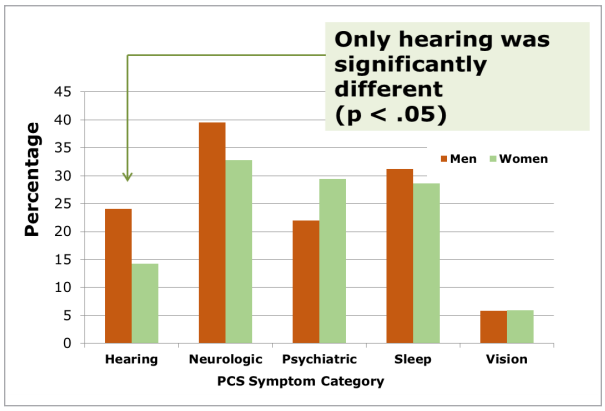


FIGURE 7-43: Post-concussion Syndrome (PCS) Symptom Rates (Figure used with permission from the authors).

Identification of significant PCS symptoms may lead to a clinical algorithm that can predict those at greater risk for reduction in QOL, which could identify areas for refinement in resource allocation and clinical treatment protocols.

This effort was supported by the Navy Bureau of Medicine and Surgery under the Wounded, Ill, and Injured Program.

Factors That Contribute to Mental Health and Quality of Life in Combat-injured Military Women

As women enter roles in the military directly related to combat operations, they have greater risk of physical injury. Exposure to physical trauma can lead to psychological sequalae. For the purpose of prevention and treatment, it is important to identify the types of psychological issues that military women may face postinjury. To this end, researchers at the Naval Health Research Center (San Diego, CA) examined the prevalence of mental

health conditions among female Service members one-year post-injury and analyzed factors which may place women at greater risk for mental health concerns and lower QOL. A total of 1,012 U.S. Service women, who sustained a combat-related injury in Iraq and Afghanistan between January 2003 and December 2015, were examined. Within the first-year post-injury, 404 women (40 percent) were diagnosed with at least one mental health disorder. The most common were post traumatic stress (20 percent), depressive (12.1 percent), adjustment (9 percent), and anxiety disorders (8 percent). Women with minor or moderate injuries were less likely to be diagnosed with a mental health disorder than women with severe injuries. Military occupations in combat support and communications were predictive of fewer mental health issues in injured women. Enlisted rank contributed to increased odds of mental health issues post-injury. Evaluation of QOL for 208 injured women in the cohort revealed that officers had a higher QOL compared with enlisted women. Women in the Air Force also had a higher QOL post-injury than those in the Army, Marines, or Navy. Women with mental health diagnoses post-injury had significantly lower QOL scores compared with those without mental health diagnoses. This study shows that combat-related injury has an impact on the mental health of a significant portion of women revealing a need to develop strategies to preserve optimal mental health and promote resiliency.

This effort was supported by the Navy Bureau of Medicine and Surgery under the Wounded, Ill, and Injured Program.

Long-term Quality of Life Outcomes in Injured U.S. Military Personnel: The Wounded Warrior Recovery Project

To better understand the effects of blast-related combat injuries on long-term health and readiness, the Naval Health Research Center (NHRC; San Diego, CA), is longitudinally assessing clinical, rehabilitative, and patient-reported outcomes in injured U.S. Service members through the Wounded Warrior Recovery Project (WWRP). WWRP is a 15-year, prospective, population-based study, with participants completing follow-up assessments every 6 months. WWRP enrollment is ongoing and each of the more than 52,000 Service members injured in Iraq and Afghanistan will be invited to participate in the study. To date, 5,575 injured Service members have provided informed consent and enrolled in the study and over 24,000 assessments have been completed; approximately 79 percent of respondents were injured in a blast event.

The study includes longitudinal assessments of patient-reported PTSD and depression symptoms and health-related QOL. Several cross-sectional assessments have been deployed, allowing the research team to examine social support, chronic pain, and functioning and satisfaction ratings for orthotic and prosthetic users. Recently, the WWRP team added longitudinal assessments related to health behaviors such as sleep, physical activity, and alcohol and tobacco use. Measures are chosen with the aim of examining the complex relationship between physical and mental health and its impact on QOL.

WWRP findings from the past year continue to demonstrate that PTSD and depression are prevalent issues facing injured Service members (*Woodruff et al., 2018*). Both can impact overall QOL, and poor mental health in particular may be a primary driver in reduced QOL (*McCabe et al., 2018; Woodruff et al., 2018*). Chronic low back pain also appears to be a prevalent issue in this population. Notably, individuals experiencing pain have higher rates and severity of PTSD and depression as well as lower QOL than those not experiencing pain (*Watrous et al., 2017; Watrous et al., 2018*). The project's public facing website is www.wwrecoveryproject.org.

This effort is supported by the Navy Bureau of Medicine and Surgery under the Wounded, Ill, and Injured Program and EACE.

Photo credit (opposite page): Pfc. William Chockey/U.S. Marine Corps


KNIPP
KNIPP

Vision Rehabilitation

Identification of Evidence Supporting the Use of Colored Filters While Reading for Patients with Blast-related Visual Problems

Approximately half of TBI patients report developing difficulties while reading such as blurring words, eye fatigue, and difficulty tracking words as one moves along a sentence. To address this issue, investigators at the University of Minnesota, Twin Cities (Minneapolis, MN) examined the effect of colored film overlays on reading speed in veterans with TBI. The study involved Veterans with TBI performing a reading speed test with and without colored films laid over the text. They looked at text with each of 10 different colored overlays and performed the reading speed test with whichever color they preferred most.

Reading speed improved significantly when colored overlays were used by Veterans with TBI compared to healthy individuals. The ratio of reading speed while using the overlays compared to reading without the overlays was significantly related to a person's convergence insufficiency (the inability of a person's eyes to work together when looking at close objects, like words on a page). People who reported more problems with convergence insufficiency tended to be helped more by the colored overlays (Figure 7-44).

Convergence insufficiency can often be treated with significant, long-term physical therapy, but these results suggest that a simple, inexpensive treatment in the short-term using colored overlays or colored lenses while reading can be effective. Because convergence insufficiency often develops after a TBI, this could be particularly helpful for people who have suffered a blast-related head injury, and research suggests that TBI patients have a larger improvement in reading speed thanks to overlays than do healthy controls.

This effort was managed by CDMRP with support from the PH/TBIRP and programmatic oversight by CRMRP/JPC-8.

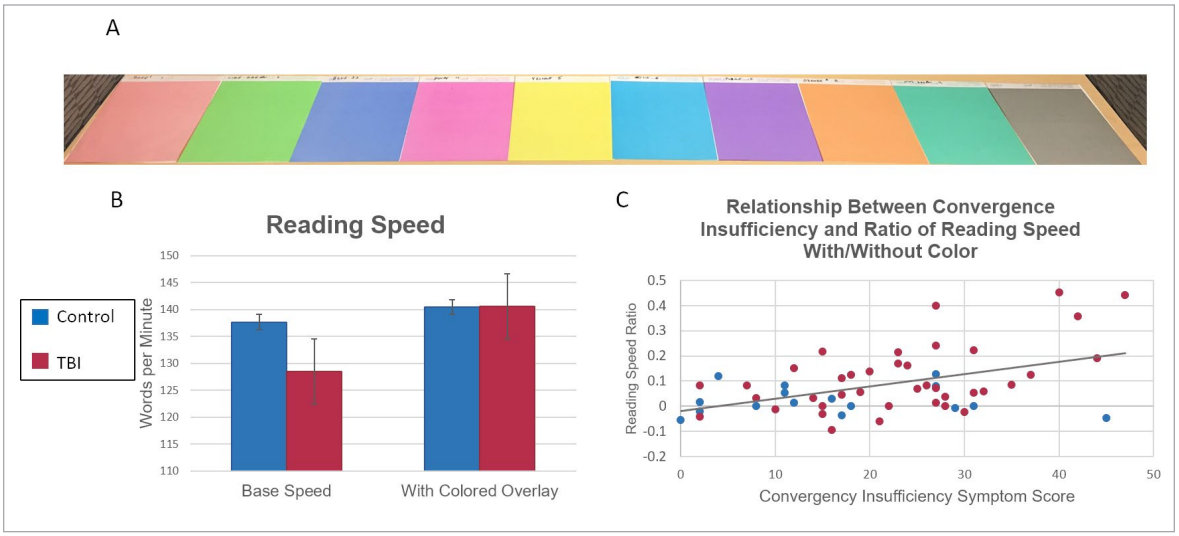


FIGURE 7-44: A) The range of colored film overlays used in this study. B) There was a significant interaction between the difference in reading speed with and without using a colored overlay and whether a Veteran had been previously diagnosed with a TBI. The TBI group showed greater improvement in reading speed when using the overlay than did healthy controls. C) The ratio of reading speed improvement with the colored overlay (difference in with and without overlay speed divided by the without speed) was significantly correlated with score on a measure of convergence insufficiency. (Figure used with permission from the authors).

Photo credit: Staff Sgt. Michael Sword/U.S. Army

Conclusion

It is an honor for the PCO to share so many accomplishments from across the blast injury research community in FY18. The breadth of research topics and outcomes is truly astounding, and it should inspire confidence among Service members, their Families, and the general public that major advances are being made to protect each Service member from potential blast injuries, and support the injured throughout their treatment and recovery processes. Collaboration across the community–both domestically and internationally–continues to enhance the knowledge base on the spectrum of blast injuries and leads to evidence-based clinical guidelines, programs, and products for blast injury prevention, mitigation, and treatment. The PCO will continue to support the mission of the EA in coordinating medical research that forms the foundation for the programs and products that target blast injuries. By disseminating information on FY18 accomplishments, the PCO encourages collaboration among the research community and builds confidence in the efforts of the Blast Injury Research Program and its domestic and international partners.

08

CHAPTER 8:

WAY FORWARD

The Blast Injury Research Program Coordinating Office (PCO) neither conducts nor finances research and development. It does not field test new technologies, nor offer clinical rehabilitation services to wounded warriors. The outstanding research results overviewed in the previous chapter are generated by talented and dedicated people throughout the U.S. Department of Defense (DoD) and its partner agencies and nations. This office coordinates blast injury research efforts by facilitating collaboration and the sharing of knowledge among researchers. ***Coordination is inherently a forward-looking function.*** Rather than respond to the exigencies of a narrowly-defined research problem or the particular circumstances of a current conflict, the PCO helps to shape efforts toward the long-range goals of Public Law 109-163 Section 256, ensuring that all these individual efforts are pulling together to enhance the prevention, mitigation, and treatment of blast injuries for the well-being of the American warfighter. Because the DoD research community recognizes the importance of this coordination function to success on battlefields of the future, the PCO receives enthusiasm, participation, and consultation from leaders throughout the research community, even in the absence of funding control or direct authority over their offices.

Outlook for Fiscal Year 2019 (FY19)

Some of the efforts detailed in this report, such as the North Atlantic Treaty Organization (NATO) Science and Technology Organization (STO) Human Factors in Medicine (HFM) Research Task Group (RTG) 234 are now complete, and the PCO's immediate role is one of helping to distribute the relevant documentation and provide detail to external inquiries. However, unless otherwise noted that a program has been concluded, the efforts detailed in this report are ongoing and the PCO will continue to engage and develop them in FY19.

One such effort is the NATO STO HFM-270 (RTG), a Framework for Modeling and Simulation of Human Lethality, Injury, and Impairment for Blast-Related Threats. FY19 will be a capstone year for this effort, during which the deliverables will be reviewed and finalized, resulting in another on-time, fully-realized completion of a NATO effort by the PCO. The planned deliverables include a conceptual framework for threat-to-outcome modeling and simulation of human lethality, injury, and impairment in all blast threat environments; an extensive literature review of models that might be appropriate for inclusion in that framework; a robust repository of information about existing models and modeling capabilities; a comprehensive dictionary of modeling and simulation terms to enhance communicating and collaboration among diverse NATO communities and disciplines; and a detailed plan for a follow-on RTG to develop validation criteria and approaches for implementing the framework. In order to realize this significant advance in computational modeling of blast injury, three meetings are scheduled for the coming year, in South Africa, Sweden, and France.

The Blast Injury Prevention Standards Recommendations (BIPSR) Process (Chapter 4) is a remarkable achievement for the DoD, as the first inclusive, stakeholder-driven process, incorporating feedback from broadly selected subject matter experts, to generate scientifically and medically valid and objective standards for protecting Service members from blast injuries. As such, it remains an important area of PCO effort for years to come. In FY19, the PCO will continue to execute the BIPSR Process for the Auditory and Dermal Burns Blast Injury Types, to prove out the Interactive Blast Injury Prevention Standards Recommendation (iBIPSR) capability using the Auditory Blast Injury Type as an exemplar, and to initiate execution of the remaining Blast Injury Types

Photo credit (opposite page): Spc. Josselyn Fuentes/U.S. Army

as ranked by the reprioritization effort. The PCO also anticipates enhancing the iBIPSR capability through stakeholder and subject matter expert (SME) feedback in support of identifying the best available, scientifically sound candidate standards to protect Service members from the entire spectrum of blast injuries. Facilitating collaboration and promoting partnerships with international partners.

The Japan-U.S. Forum on Blast Injury will launch the newly christened International Forum on Blast Injury Countermeasures (IFBIC) in FY19. IFBIC 2019, May 8-10, 2019, will host an international assembly focused on multi-disciplinary science and medicine necessary to increase understanding of blast injury. The forum will feature discussions of innovative research on broad blast-injury-related topic areas to include blast injury epidemiology; environmental sensing of blast wave hazards; primary blast injury; secondary and tertiary blast injury; long-term effects, cumulative effects, and chronic symptoms due to blast exposure; prevention, mitigation, and treatment of blast injuries; diagnostic measures and biomarkers; computational modeling and simulation of blast phenomena and blast injury; and new technology and methods for blast injury research and medicine. This comprehensive agenda enables the new, larger blast injury research community to build on the successes of past meetings.

The Brain Health Research Program Coordinator will continue in FY19 to be actively involved with the worldwide brain health community, enhancing DoD awareness of cutting-edge brain injury science and seeking opportunities to advance the prevention, mitigation, and treatment of warfighter brain injuries. One particularly rich forum for this endeavor is the 2019 International Brain Injury Association World Congress, March 2019, in Toronto. At this meeting, international professionals will present information on the care of persons with acquired brain injury and/or the science of brain injury, and present state-of-the-art research on topics ranging from basic science to clinical aspects of brain injury. The program will feature internationally recognized invited speakers, platform lectures, panels, workshops, and selected oral presentations and posters. Another planned key engagement is the Annual International Initiative for Traumatic Brain Injury Research (InTBIR) Meeting scheduled for October 2019. InTBIR is a cooperative effort of the European Commission (EC), the Canadian Institutes of Health Research (CIHR), and the National Institutes of Health (NIH) to coordinate and leverage clinical research activities on traumatic brain injury (TBI) research. InTBIR is designed to improve health care and lessen the global burden of TBI by 2020 through the discovery of causal relationships between treatments and clinically meaningful outcomes.

The Neuroscience, Neurotrauma, and Neurodegeneration Working Group (N3WG), stood up in FY18 through the efforts of the PCO and the Brain Health Research Program Coordinator, will continue to develop its processes in FY19 and will formalize its charter. Because of the intense public and military interest in brain injury, the U.S. Army Medical Research and Materiel Command (USAMRMC) neuroscience community is extensively and urgently queried: the N3WG responded to scores of informational taskers in FY18 and expects to handle many more, so the processes for rapid and concerted response, enabling the diverse elements of this community to speak with a single corporate voice encompassing its vast experience and knowledge, will be continually refined. The process for a rapid and concerted response to taskers enables the diverse elements of this community to speak with a single corporate voice, with vast experience and knowledge.

Photo credit: Spc. Fred Brown/U.S. Army

The N3WG is also finding other ways to leverage its collective expertise. For example, the N3WG standardized processes to share notes with members and outside discussions during the Military Health Sciences Research Symposium (MHSRS) conferences. The N3WG continues to receive briefings from three or four outside vendors and/or researchers each month, expanding military awareness of the tools and therapies available to protect and preserve warfighter brain health.

The PCO-sponsored **International State-of-the-Science (SoS) meetings** will continue as an essential tool for canvassing the multidisciplinary research community from government, industry, and academia to share expertise and research at the boundaries of current understanding, and to make recommendations for the best priorities and focus areas for ongoing DoD blast injury research. The March 2019 State-of-the-Science meeting on "Limb Salvage and Recovery after Blast-related Injury" will focus on severe blast-related limb injury and outcome. The meeting's objectives will be to describe the epidemiology and outcomes of limb salvage after severe blast-related limb injury, to review the evidence regarding the decision to salvage versus to amputate a limb after severe blast-related limb injury, to review evidence and innovations regarding rehabilitation, reintegration, and recovery after limb salvage; and to recommend priorities for emerging research, technology, and policy gaps pertaining to limb salvage, restoration, and recovery. This meeting will give DoD program managers and leaders valuable tools to evaluate the most productive and required research for limb salvage for blast-injured Service members in future conflicts.

Coordination of Effort

To illustrate the role of the PCO in charting the way forward for military blast injuries, consider a single Soldier's encounter with blast injury. Perhaps, in a devastating injury all too common during Operation Enduring Freedom (OEF), a Soldier encounters an improvised explosive device (IED) while patrolling on foot through rocky Afghan terrain, suffering a traumatic lower limb amputation and other blast-related damage. As this Report has made clear, the event, its buildup, and its consequences can be understood through a myriad of perspectives, each taken by a different part of the blast injury research community. Consider just a small fraction of these:

- The Soldier has been protected in theater, first and foremost, by his professional adherence to and intensive training in tactics, techniques, and procedures enacted in response to information constantly collected and disseminated by organizations like Joint Trauma Analysis and Prevention of Injury in Combat (JTAPIC) (p. 35) and the Center for Army Lessons Learned.

- The Soldier is also surrounded by a web of detection and communication technologies to alert him to danger, such as the Joint Program Office Joint Project Office for the Joint Light Tactical Vehicles (JPO/JLTV) integrated blue force tracker and tactical ground reporting system (p. 102).

- The Soldier encounters the IED equipped with the latest personal protective equipment (PPE), with designs informed by studies such as the Army Research Laboratory's (ARL) investigation of fabric designs that protect against IED blast (p. 101) and tested on platforms like the Naval Research Laboratory (NRL)/Walter Reed Army Institute for Research (WRAIR) GelMan head surrogate (p. 98). Additionally, the Soldier may even be protected by prophylactic drugs or supplements, as suggested by the WRAIR study on dietary modifications that may be neuroprotective (p. 106).

- Cutting-edge simulation and modeling have given insight into what happens to the Soldier at the instant of the blast. Examples include the polymer models from the San Antonio Military Medical Center (SAMMC), the New Mexico Tech Department of Chemical Engineering, and Michigan State University Department of Mechanical Engineering that can be optically probed at high speed during simulated blasts (p. 99), or the University of Oklahoma's real-time modeling of blast wave effects in the ear (p. 103).

- The devastating effects upon the Soldier in the immediate aftermath of the blast are also extensively studied, by accomplishments such as the New Jersey Institute of Technology's (NJIT) rodent models of blast injury (p. 105) and/or the human injury risk curve models developed with cadaver studies at the Medical College of Wisconsin (p. 87).

- In the aftermath of the blast, the Soldier's buddies, front-line medics, and forward-deployed surgical teams will be able to use a formidable array of treatment options now in development, including drag-reducing polymer-containing fluids for shock mitigation that reduce the risk of TBI, developed at the University of New Mexico Health Sciences Center and the University of Pittsburgh (p. 109), or easily stored and transported synthetic transfusion media like the SynthoPlate from Case Western Reserve University, the University of Pittsburgh, and the U.S. Army Institute for Surgical Research (USAISR) (p. 110). Early interventions will be guided by studies like those at the Hôpital du Sacre-Coeur de Montréal (p. 147) of which surgeries produce better neurologic outcomes for blast victims.

- When the Soldier is brought back to a higher level of care, he/she will be examined for unseen injuries like TBI using novel tests like the blood test under development by Banyan Biomarkers (p. 115), and provided options for more complex surgical interventions, perhaps targeting pathways identified by the Drexel University team to forestall spinal cord injury-related respiration deficits (p. 122), or repairing damaged nerves with technology developed at Axogen (p. 128). Military caregivers continue to seek to forestall life-threatening infections with the latest Joint Trauma System (JTS) clinical practice guidelines (Chapter 5), and with the aid of tools like the novel antimicrobial nanoemulsions being developed at the University of Michigan (p. 125).

- As the Soldier begins the long road to recovery, he/she will have access to the latest, most functional prostheses, like the running-specific leg prostheses being developed at the University of Colorado Boulder with the Veterans Affairs (VA) Eastern Colorado Health Care System (ECHCS) Jewell Clinic Regional Amputation Center (p. 139). Pain control devices like the peripheral nerve stimulation devices from SPR Therapeutics (p. 141) may aid the transition.

- Ultimately the injured Soldier may transition back into service if tools like the Center for the Intrepid's Readiness Evaluation (p. 148) establishes fitness for duty. Alternately he/she may pursue further rehabilitation as a Veteran and assisted in his recovery by tools developed through the long-term quality of life studies of the Naval Health Research Center's Wounded Warrior Recovery Project (p. 152) and helped to self-sufficiency and quality of life by tools like the University of Florida "DriveSafety" simulator (p. 149).

- Data about the Soldier's welfare along each step of this process, capturing multiple aspects of recovery, are collected and fed back into the Military Health System (MHS) through systems like the Trauma Infectious Disease Outcomes Survey (Chapter 5) or the University of Maryland's registry of toxicity from embedded metal fragments (p. 129), and these data will improve the tools and care for the wounded who come after.

These advances are possible because the innovative and committed researchers who enable them are each focused intently upon a single moment, process, or need: each possess deep expertise in a minute facet of blast injury and could not realize their advances without that focused mastery. However, to the Soldier, blast injury is not the milliseconds of overpressure, or the elimination of a single infection, or the fitting of a prosthesis. It is a months- or decades-long, arduous journey that begins with rigorous training and deployment and ends with the resolute struggle to regain function and personal fulfilment, to transcend injury. Each step in this process is connected and influences the others, and progress depends on balancing the Soldier's resources and needs while moving forward.

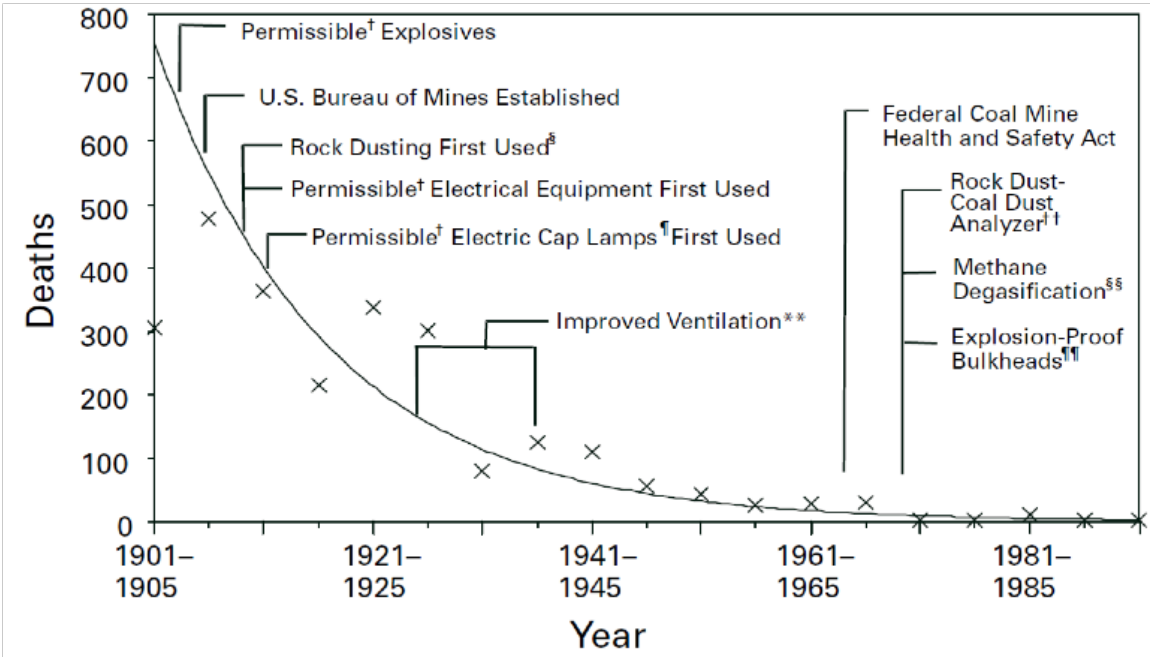
The PCO exists to support the DoD to understand blast injury as the Soldier understands it – as a coherent and connected whole that depends on complex trade-offs. Each piece of the research affects the others: PPE or vehicle design, for example, affects the patterns of injury that must be addressed in urgent care; modeling efforts should be driven by on-the-ground needs; treatment options are responsive to new diagnostic tests; and medical care of the wounded warfighter is informed by data collected from reintegrating Veterans. DoD requires a comprehensive view across all blast-related mitigation, treatment, and reset efforts, with an awareness of the current state of the science

and expert analysis of the most necessary and productive investments, in order to balance the PCO's limited resources among them. Most importantly, all efforts are ultimately subordinate to classic military considerations of mission, enemy, terrain, climate, troops available, time, and civilian considerations. By coordinating efforts, the PCO ensures that as each research group continues to progress along its own track and to solve its particular issues, the DoD as a whole continues to make meaningful progress on the overarching goal of the prevention, mitigation, and treatment of blast injury, in much the same way as timing and coordination enable the cylinders of an engine, each in its own cycle, to move an entire system forward.

The Road Ahead

Considering the costs borne by the American Warfighter, forward motion towards the PCO mission may seem unacceptably slow. It is comforting, however, to consider progress in blast injuries in civilian settings. Deaths due to mine explosions declined more than a hundred-fold over the twentieth century (Figure 8-1; *Centers for Disease Control and Prevention, 1999*), from an average of 477 per year in 1906-1910, to fewer than three per year in 1991-1995. Employment in mining only dropped about five- or six-fold between 1910 and 2000, so that is a remarkable gain, but, as the chart shows, it was a gain achieved in fits and starts as new ideas and new technologies were rolled out over a century.

FIGURE 8-1: Five-year averages of annual number of deaths related to coal mine explosions in the United States, 1901-1995. (*Centers for Disease Control and Prevention, 1999*)



*	Each X represents the 5-year average of number of deaths resulting from explosions; the line is a smoothed regression through the 5-year averages.
†	Explosives and equipment that can be used in an explosive methane-rich environment without causing a methane explosion.
§	The process of applying a layer of rock dust over the coal dust, which creates an inert mixture and inhibits a coal dust explosion.
¶	Lamps worn on minors' caps.
**	Ventilation improvements, including the use of reversible fans, reducing concentration of methane and removing explosive gas from the mine.
††	A hand-held monitor that provides instantaneous readings of the rock-to-coal dust mixture to ensure that it is inert.
§ §	Techniques to remove methane from the coal bed before mining the coal.
¶ ¶	Explosion-proof walls used to seal abandoned (mined-out) areas to protect workers in active parts of the mine.

Photo credit: Courtesy Photo/U.S. Army

Warfighter blast injury is a vastly more complex problem, with more sources of injury, a dynamically changing threat environment, and enemies that can adapt to countermeasures over time by developing better targeted or more lethal weapons. That DoD has been able to generate the powerful array of technologies and innovations featured in this Report in the dozen years since the creation of the Executive Agent (EA), a remarkable testament to the talent and dedication of its medical and nonmedical research community.

Blast injury will be a looming danger as long as we deploy Service members to combat zones, and the ever-evolving battlefield demands constant and thoughtful coordination of research assets. Congress anticipated this need in Section 256 of Public Law 109-163, where the very first enumerated responsibility of the EA is planning: anticipating the future threat. The PCO's vision, "*To establish and maintain a fully coordinated DoD blast injury research program as envisioned by Congress and directed by the Secretary of Defense, that delivers timely and effective blast injury prevention, mitigation, and treatment strategies to our Service members today and in the future*," recognizes that ongoing need. The researchers and programs featured in this Report are at the forefront of addressing blast injuries, and it is an honor to be able to share their diverse accomplishments from FY18. The deep expertise and commitment to innovation reflected in those accomplishments should inspire confidence among Service members, their Families, and the Nation, that the DoD is working tirelessly to protect our warriors from the threat of blast injury, and support the injured through their treatment, recovery, and return to productive and happy lives. The PCO will continue to fortify the mission of the EA by coordinating medical and non-medical research that advances these goals and that forms the foundation of the programs and products that treat, mitigate, and prevent blast injury. By encouraging collegiality and coordination among these remarkable researchers, the PCO will ensure that their efforts will make lasting contributions to the mission, the Nation, and its Service men and women today, tomorrow, and beyond.

APPENDIX A:

ACRONYMS

A

A1C	Airman First Class
AAMTI	AMEDD Advanced Medical Technologies Initiative
AE	Above Elbow
AFB	Air Force Base
AFFD	Auditory Fitness for Duty
AFIRM	Armed Forces Institute of Regenerative Medicine
AFMC	Air Force Materiel Command
AFMS	Air Force Medical Service
AFRL	Air Force Research Laboratory
AHAAH	Auditory Hazard Assessment Algorithm for Humans
AHD	Army Hearing Division
AHI	Apnea-hypopnea Index
AI	Artificial Intelligence
AIS	American Spinal Injury Association Impairment Scale
AMC	Army Materiel Command
ANORs	Allowable Number of Rounds
ALT	Acquisition, Logistics, and Technology
ANOVA	Analysis of Variance
APHC	Army Public Health Center
ARL	Army Research Laboratory
ARL/SLAD	Army Research Laboratory Survivability/Lethality Analysis Directorate
ASA	Assistant Secretary of the Army
ASA(ALT)	Assistant Secretary of the Army for Acquisition, Logistics, and Technology
ASBREM	Armed Services Biomedical Research, Evaluation, and Management
ASD	Assistant Secretary of Defense
ASD(HA)	Assistant Secretary of Defense for Health Affairs
ASD(R&E)	Assistant Secretary of Defense for Research and Engineering
ASIA	American Spinal Injury Association
ASSIST	Acquisition Streamlining and Standardization Information System
ATC	Aberdeen Test Center
ATLA	Acquisition, Technology, and Logistics Agency
Aβ	Amyloid Beta

B

BAA	Broad Agency Announcement
BADER	Bridging Advanced Developments for Exceptional Rehabilitation
BAMC	Brooke Army Medical Center
BASIC	Brain and Spinal Injury Center
BBB	Blood Brain Barrier
BDR	Biodynamic Data Resource
BE	Below Elbow
BHSAI	Biotechnology High Performance Computing Software Applications Institute
BIMM	Blast-induced Injury Mechanisms and Model
BIPSR	Blast Injury Prevention Standards Recommendation
BOP	Blast Overpressure
BOP-HHA	Blast Overpressure-Health Hazard Assessment
BRAID	Blast Related Auditory Injury Database
BRI	Blast-related Injury
BSM	Brier Score Metric
bTBI	Blast-induced Traumatic Brain Injury
BTS	Blast Test Site
BUMED	Bureau of Medicine and Surgery
BWIs	Ballistic Wound Infections

C

C5	Component 5
CAD	Computer Aided Design
CAP	Consortium to Alleviate PTSD
Capt	Captain/U.S. Air Force
CARE	Concussion Assessment, Research, and Education

Photo credit (opposite page): Staff Sgt. Jonathan Lovelady/U.S. Air Force

CAVRN	Collaborative Auditory Vestibular Research Network
CB2	Cannabinoid Type-2 Receptor
CCC	Combat Casualty Care
CCCRP	Combat Casualty Care Research Program
CCL22	C-C Motif Chemokine Ligand 22
CDC	Centers for Disease Control and Prevention
CDER	Center for Drug Evaluation and Research
CDISC	Clinical Data Interchange Standards Consortium
CDMRP	Congressionally Directed Medical Research Programs
CDRH	Center for Devices and Radiological Health
CENC	Chronic Effects of Neurotrauma Consortium
CFUs	Colony-forming Units
cGMP	Current Good Manufacturing Practices
CI	Confidence Interval
CIHR	Canadian Institutes of Health Research
cm	Centimeter
CNRM	Center for Neuroscience and Regenerative Medicine
COA	Clinical Outcome Assessment
COCOM	Combatant Command
CoE	Center of Excellence
COI	Community of Interest
COTS	Commercial Off The Shelf
CPG	Clinical Practice Guidelines
Cpl	Corporal
CPT	Captain/U.S. Army
CRADA	Cooperative Research and Development Agreement
CRM	Clinical and Rehabilitative Medicine
CRMRP	Clinical and Rehabilitative Medicine Research Program
CRSR	Center for Rehabilitation Sciences Research
CSF	Cerebrospinal Fluid
CSO	Collaboration Supporting Office
CT	Computed Tomography
CTA	Composite tissue Allotransplantation
CTAs	Computed Tomography Angiograms

D

DAE	Dynamic Air Exchange
dAMP	Designed Antimicrobial Peptides
DARPA	Defense Advanced Research Projects Agency
DASA(DEC)	Office of the Deputy Assistant Secretary of the Army for Defense Exports and Cooperation
DCoE	Defense Center of Excellence for Psychological Health and Traumatic Brain Injury
DDESB	DoD Explosives Safety Board
DDT	Drug Development Tool
DHA	Defense Health Agency
DHA R&D	Defense Health Agency Research and Development
DHHS	Department of Health and Human Services
DIPR	Defence Institute of Psychological Research
dL	Deciliter
DMRDP	Defense Medical Research and Development Program
DoD	Department of Defense
DoDD	Department of Defense Directive
DRDO	Defence Research and Development Organization
D-RFA	Delayed Removal from Activity
DRP	Drag Reducing Polymers
DRP-RF	Drag Reducing Polymers to the Resuscitation Fluid
DTI	Diffusion Tensor Imaging
DTRA	Defense Threat Reduction Agency
DTTI	Defense Trade and Technology Initiative
DVBIC	Defense and Veterans Brain Injury Center

E

EA	Executive Agent
EAB	Expert Advisory Board
EACE	Extremity Trauma and Amputation Center of Excellence
EC	European Commission
ECHCS	Eastern Colorado Health Care System
EDA	Electrodermal Activity
ELISA	Enzyme-linked Immunosorbent Assay
EMED	Expeditionary Medical Encounter Database
ENIGMA	Enhancing Neuroimaging Genetics through Meta-Analysis
EOD	Explosive Ordinance Disposal
ERDC	Army Engineer Research and Development Center
ESBL	Extended Spectrum Beta-Lactamases
ESKAPEE	Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, Enterobacter species, and Escherichia coli
ESiT	Environmental Sensors in Training

F

FDA	U.S. Food and Drug Administration
FDP	Freeze Dried Plasma
FE	Finite Element
FEA	Finite Element Analysis
FedBizOpps	Federal Business Opportunities
FEM	Finite Element Model
FFP	Fresh Frozen Plasma
FFRDC	Federally Funded Research and Development Center
FITBIR	Federal Interagency Traumatic Brain Injury Research
FMS	Functional Movement Screen
FY	Fiscal Year

G

GE	General Electric
GFAP	Glial Fibrillary Acidic Protein
GWIRP	DoD Gulf War Injury Research Program

H

HA	Health Affairs
HAV	Human Acellular Vessel
HCE	Hearing Center of Excellence
HDIAC	Homeland Defense and Security Information Analysis Center
HExCAT	Homeland Explosives Consequence Assessment Tool
HFM	Human Factors and Medicine
HHA	Health Hazard Assessment
HHS	Department of Health and Human Services
HIPC	Human Injury Probability Curve
HMGB1	High Mobility Group Box 1
HDIAC	Homeland Defense and Security Information Analysis Center
HS	Hemorrhagic Shock

I

iBIPSR	Interactive Blast Injury Prevention Standards Recommendation
IDCRP	Infectious Disease Clinical Research Program
IDEO	Intrepid Dynamic Exoskeleton Orthosis
IED	Improvised Explosive Device
IExTRAWG	Inter-Agency Explosive Terrorism Risk Assessment Working Group
IFBIC	International Forum on Blast Injury Countermeasures
IFI	Invasive Fungal Infection
IL	Interleukin
IL-1β	Interleukin -1beta
IL-18	Interleukin -18
IND	Investigational New Drug
INMAS	Institute of Nuclear Medicine and Allied Sciences-DRDO

INMAS-DRDO	Institute of NuclearMedicine and Allied Sciences Ministry of Defence, India
InTBIR	International Initiative for Traumatic Brain Injury Research
INTRuST	The INjury and TRaumatic STress
IOM	Institute of Medicine
IPRs	In-Progress Reviews
IPT	Integrated Product Team
IRBA	Institute de Recherche Biomedical des Armees
IRC	Injury Risk Curves
I-RFA	Immediate Removal From Activity
ISS	Injury Severity Score
ITBRL	Indian Terminal Ballistic Research Laboratory
IV&V	Independent Verification & Validation

J

JBER	Joint Base Elmendorf-Richardson
JHU/APL	Johns Hopkins University Applied Physics Laboratory
JIDA	Joint Improvised-Threat Defeat Agency
JMoD	Japan Ministry of Defense
JNLWP	Joint Non-Lethal Weapons Program
JPC	Joint Program Committee
JPO	Joint Project Office
JPO JLTV	Joint Project Office for the Joint Light Tactical Vehicles
JSDF	Japan Self-Defense Forces
JTAPIC	Joint Trauma Analysis and Prevention of Injury in Combat
JTG	Joint Technology Group
JUFBI	Japan-U.S. Technical Information Exchange Forum

K

kg	Kilogram
KIA	Killed in Action
km	kilometer
kPa	Kilopascal (unit of pressure)

L

LBP	Lower Back Pain
LCpl	Lance Corporal/U.S. Marine Corps
LE	Lower Extremity
LES	Lumbar Erector Spinae
LLA	Lower Limb Amputation
LPA	Lysophosphatidic Acid
LRMC	Landstuhl Regional Medical Center

M

MAAWS	Multipurpose Anti-Tank/Anti-Personnel Weapons System
MAR1	Maresin 1
MARP	Military Amputee Research Program
MAUT	Multi-Attribute Utility Theory
mBESS	Balance Error Scoring System
MDDT	Medical Device Development Tools
MDRO	Multidrug-Resistant Organisms
MDR/VO	Multidrug-Resistant and Virulent Organisms
MEASSuRE	Mechanical Stretcher
MEDCOM	U.S. Army Medical Command
MEMC	Middle-ear Muscle Contraction
MEP	Motor Evoked Potential
METRC	Major Extremity Trauma Research Consortium
mg	Milligrams
mg/dL	Milligrams/deciliter
MHS	Military Health System
MHSRS	Military Health System Research Symposium
MIDRP	Military Infectious Disease Research Program
MIL-STD	Military Standard
MIT	Massachusetts Institute of Technology
MMP3	Matrix Metalloproteinase 3
MOM	Military Operational Medicine
MOMRP	Military Operational Medicine Research Program
MOS	Military Occupational Specialty
MPa	Megapascal

MPs	Microparticles
MRI	Magnetic Resonance Imaging
MRS	Magnetic Resonance Spectroscopy
MSG	Master Sergeant/U.S Army
MSgt	Master Sergeant/U.S. Air Force/ U.S. National Guard
MRSA	Methicillin-resistant Staphylococcus aureus
MSISRP	Medical Simulation and Information Systems Research Program
mTBI	Mild Traumatic Brain Injury

N

N3WG	Neuroscience, Neurotrauma, and Neurodegeneration Working Group
NASA	National Aeronautics and Space Administration
NATO	North Atlantic Treaty Organization
NAVAIR	Naval Air Systems Command
NB-201	Nanoemulsion Formulations
NBRI	Non-Blast-Related Injury
NCAA	National Collegiate Athletic Association
NCTH	Non-compressible Truncal Hemorrhage
NDAA	National Defense Authorization Act
NDMC	National Defense Medical College
NFH	Neurofilament Heavy Chain
NFL	National Football League
NGIC	National Ground Intelligence Center
NHP	Nonhuman Primates
NHRC	Naval Health Research Center
NIAID	National Institute of Allergy and Infectious Diseases
NICoE	National Intrepid Center of Excellence
NIH	National Institutes of Health
NIHL	Noise Induced Hearing Loss
NJIT	New Jersey Institute of Technology
NM/DD	Nightmares and Disturbing Dreams
NMDA	N-methyl-D-aspartate
NMRC	Naval Medical Research Center
NOX1	Nicotinamide Adenine Dinucleotide Phosphate Oxidase 1
NOX2	Nicotinamide Adenine Dinucleotide Phosphate Oxidase 2
NRAP	National Research Action Plan
NRL	Naval Research Laboratory
NSF	National Science Foundation
NSMRL	Naval Submarine Medical Research Laboratory
NSWC	Naval Surface Warfare Center
NSWC CD	Naval Surface Warfare Center, Carderock Division
NSWC IHD	Naval Surface Warfare Center, Indian Head Division

O

OASD(HA)	The Office of the Assistant Secretary of Defense for Health Affairs
OBTT	Operation Brain Trauma Therapy
OBTT-ES	Operation Brain Trauma Therapy-Extended Studies
OEF	Operation Enduring Freedom
OIF	Operation Iraqi Freedom
OND	Operation New Dawn
ONR	Office of Naval Research
OPUS	Orthotics and Prosthetics Users' Survey
OR	Odds Ratio
ORISE	Oak Ridge Institute for Science and Education
OSD	Office of the Secretary of Defense
OT	Occupational Therapy

P

PA	Project Arrangement
PAA	Principal Assistant for Acquisition Office
PAR&T	Principal Assistant for Research and Technology Office
PCL	Posttraumatic Stress Disorder Checklist
PCL-5	PTSD Checklist Version 5
PCO	Program Coordinating Office
PCR	Polymerase Chain Reaction
PCS	Post-concussive Syndrome
PDHA	Post-Deployment Health Assessment
PEO	Program Executive Office
PEO CS&CSS	Program Executive Office Combat Support and Combat Service Support
PH	Psychological Health
PH/TBI	Psychological Health/Traumatic Brain Injury
PH/TBIRP	Psychological Health/Traumatic Brain Injury Research Program
PHQ-9	Patient Health Questionnaire-9
PI	Principal Investigator
PIHL	Pharmaceutical Interventions for Hearing Loss
PNS	Peripheral Nerve Stimulation
PoW	Program of Work
PPE	Personal Protective Equipment
PRMRP	Peer Reviewed Medical Research Program
PROOVIT	PROspective Observational Vascular Injury Trial
PRORP	Peer Reviewed Orthopedic Research Program
psi	Pounds Per Square Inch
PTSD	Posttraumatic Stress Disorder
P13	Anti-inflammatory Peptide

Q

QoL	Quality of Life
QUADAS-2	Quality Assessment of Diagnostic Accuracy Studies 2

R

R&A	Review & Analysis
R&D	Research & Development
R&E	Research & Engineering
RBC	Red Blood Cells
RDECOM	Research, Development, and Engineering Command
RDECOM ITC-PAC	Research, Development, and Engineering Command International Technology Center-Pacific
RDT&E	Research, Development, Testing, & Evalulation
REBOA	Resuscitative Endovascular Balloon Occlusion of the Aorta
REDOp	Readiness Evaluation During Simulated Dismounted Operation
RF	Resuscitation Fluids
RFI	Request for Information
ROC	Required Operational Capability
ROK	Republic of Korea
RSA	Respiratory Sinus Arrhythmia
RSP	Running-specific Prosthesis
RTD	Return to Duty
RTD&E	Research, Development, Testing, & Evaluation
RTG	Research Task Group
RTRP	Reconstructive Transplant Research Program

S

S&T	Science and Technology
S2S	U.S.-Japan Service to Service
SAHA	Suberoylanilide Hydroxamic Acid
SAMMC	San Antonio Military Medical Center
SCI	Spinal Cord Injury
SCIRP	Spinal Cord Injury Research Program
SECARMY	Secretary of the Army
SECDEF	Secretary of Defense
Sgt	Sergeant/U.S. Air Force
SGT	Sergeant/U.S. Army
SME	Subject Matter Expert
sMEA	Stretchable Microelectrode Array

SoS	State-of-the-Science
SPIE	Society of Photographic Instrumentation Engineers
SPMs	Specialized Pro-resolving Lipid Mediators
SrA	Senior Airman/U.S. Air Force
SRT	Simple Reaction Time
SSG	Staff Sergeant/U.S. Army
SSgt	Staff Sergeant/U.S. Air Force
SSTI	Skin and Soft-tissue Infections
STO	Science and Technology Organization
STRI	Simulation, Training, and Instrumentation
STRONG STAR	South Texas Research Organizational Network Guiding Studies on Trauma and Resilience

T

T&E	Testing and Evaluation
TARDEC	U.S. Army Tank Automotive Research Development and Engineering Center
TBI	Traumatic Brain Injury
TEAM-TBI	Targeted Evaluation, Action, and Monitoring of Traumatic Brain Injury
TED	Traumatic Brain Injury Endpoints Development
TEF	Toxic Embedded Fragment
TES	Bilateral Thoracic
TGF-β	Transforming Growth Factor Beta
TIDOS	Trauma Infectious Disease Outcomes Study
TM	Tympanic Membrane
TMR	Targeted Muscle Reinnervation
TPC	Trunk Postural Control
TRACK-TBI	Transforming Research and Clinical Knowledge in Traumatic Brain Injury
Tregs	Regulatory T-cell
TRL	Technology Readiness Level
TSCI	Traumatic Spinal Cord Injury
TSG	The Surgeon General of the U.S. Army
TSgt	Technical Sergeant/U.S. Air Force
TT	Technical Team
TTAs	Transtibial Amputations

U

UBB	Underbody Blast
UCH-L1	Ubiquitin Carboxy-Terminal Hydrolase
UE	Upper extremity
UK	United Kingdom
US	United States
USAARL	U.S. Army Aeromedical Research Laboratory
USAISR	U.S. Army Institute of Surgical Research
USAMMDA	U.S. Army Medical Materiel Development Activity
USAMRMC	U.S. Army Medical Research and Materiel Command
USAPHC	U.S. Army Public Health Center
USD(AT&L)	Under Secretary of Defense for Acquisition, Technology, and Logistics
USMC	U.S. Marine Corps
USSOCOM	U.S. Special Operations Command
USU	Uniformed Services University
USUHS	Uniformed Services University of the Health Sciences
UVA	University of Virginia

V

V&V	Verification & Validation
VA	U.S. Department of Veterans Affairs
VBIED	Vehicle-born Improvised Explosive Device
VCA	Vascularized Composite Allotransplantation
VCE	Vision Center of Excellence
VOMS	Vestibular/Ocular Motor Screening

W

WG	Working Group
WIA	Wounded in Action
WIAMan	Warrior Injury Assessment Manikin
WII	Wounded, Ill, and Injured
WRAIR	Walter Reed Army Institute of Research
WRNMMC	Walter Reed National Military Medical Center
WWRP	Wounded Warrior Recovery Project

X

xAAPS	Expanded Automatic Assessment of Postural Stability

Y

YTC	Yuma Testing Center

OTHER

2D	Two Dimensional
3D	Three Dimensional

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APPENDIX B:

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APPENDIX C:

DoDD 6025.21E

Department of Defense
DIRECTIVE

NUMBER 6025.21E
July 5, 2006

USD(AT&L)

SUBJECT: Medical Research for Prevention, Mitigation, and Treatment of Blast Injuries

References: (a) Section 256 of Public Law 109-163, "National Defense Authorization Act for Fiscal Year 2006" [1]
(b) DoD Directive 5101.1, "DoD Executive Agent," September 3, 2002
(c) DoD Directive 5134.3, "Director of Defense Research and Engineering (DDR&E),"November 3, 2003
(d) DoD Directive 5025.1, "DoD Directives System," March 2005
(e) through (g), see Enclosure 1

1. PURPOSE

This Directive:

1.1. Implements Reference (a) by establishing policy and assigning responsibilities governing coordination and management of medical research efforts and DoD programs related to prevention, mitigation, and treatment of blast injuries.

1.2. Designates the Secretary of the Army, in compliance with Reference (a) and consistent with Reference (b), as the DoD Executive Agent (DoD EA) for Medical Research for Prevention, Mitigation, and Treatment of Blast Injuries according to Reference (b).

1.3. Establishes the Armed Services Biomedical Research Evaluation and Management (ASBREM) Committee. The ASBREM Committee serves to facilitate coordination and prevent unnecessary duplication of effort within DoD biomedical research and development and associated enabling research areas, to include serving as the forum for implementation of subsections (d) and (g) of Reference (a).

Photo credit (opposite page): Spc. Evangelia Grigiss/U.S. Army

2. APPLICABILITY

This Directive applies to:

2.1. The Office of the Secretary of Defense, the Military Departments, the Chairman of the Joint Chiefs of Staff, the Combatant Commands, the Office of the Inspector General of the Department of Defense, the Defense Agencies, the DoD Field Activities, and all other organizational entities in the Department of Defense (hereafter collectively referred to as the "DoD Components").

2.2. Medical and associated enabling research supported by any DoD Component for prevention, mitigation, and treatment of blast injuries.

3. DEFINITIONS

As used in this Directive, the following terms are defined as follows:

3.1. Blast Injury. Injury that occurs as the result of the detonation of high explosives, including vehicle-borne and person-borne explosive devices, rocket-propelled grenades, and improvised explosive devices. The blast injury taxonomy is provided at Enclosure 2.

3.2. Research. Any systematic investigation, including research, development, testing, and evaluation (RDT&E), designed to develop or contribute to general knowledge.

4. POLICY

It is DoD policy that:

4.1. DoD research related to blast injury prevention, mitigation, and treatment will be coordinated and managed by a DoD EA to meet the requirements, objectives, and standards of the DoD Military Health System as identified by the Under Secretary of Defense for Personnel and Readiness (USD(P&R)) and the unique combat casualty care requirements of the DoD Components.

4.2. Relevant research shall take maximum advantage of the scientific and technical capabilities of industry, academia, DoD Components, and other Federal Agencies.

4.3. The ASBREM Committee will be the venue for joint and cross-Service coordination specified by Reference (a).

4.4. DoD Components will gather and share medical information related to the efficacy of personal protective equipment and of vehicular equipment designed to protect against blast injury.

5. RESPONSIBILITIES AND FUNCTIONS

5.1. The Director of Defense Research and Engineering (DDR&E), under the Under Secretary of Defense for Acquisition, Technology and Logistics, according to DoD Directive 5134.3

(Reference (c)), shall:

5.1.1. Plan, program, and execute the functions and reports mandated for the DDR&E by Reference (a).

5.1.2. Have the authority to publish DoD Issuances consistent with Reference (d) for implementation of this Directive.

5.1.3. Establish, as needed, procedures to ensure that new technology developed under this Directive is effectively transitioned and integrated into systems and subsystems and transferred to and firmly under the control of the DoD Components.

5.1.4. Chair the ASBREM Committee to coordinate DoD biomedical research (see Enclosure 3 for additional detail), and employ that entity to facilitate the DoD EA's coordination and oversight of blast-injury research as specified in Reference (a).

5.1.5. Serve as the final approving authority for DoD blast-injury research programs.

5.1.6. Oversee the functions of the DoD EA and conduct/report on related periodic assessments (per Reference (a)).

5.2. The Assistant Secretary of Defense for Health Affairs (ASD(HA)), under the USD(P&R), shall:

5.2.1. Assist the DDR&E, the DoD EA, and the Director, Joint Improvised Explosive Devices Defeat Organization (JIEDDO), with identification of related operational and research needs, assessment of relevant research efforts, and coordination of planning to resolve capability gaps through focused research efforts.

5.2.2. Be the approving authority for Military Health System prevention and treatment standards developed and proposed by the DoD EA.

5.2.3. Appoint appropriate representatives to related coordinating boards or committees established by the DoD EA.

5.2.4. Ensure that the information systems capabilities of the Military Health System support the DoD EA and the functions specified by this Directive.

5.2.5. Serve as Co-chair of the ASBREM Committee. (See Enclosure 3 for additional detail.)

5.3. The Secretary of the Army is hereby designated as the DoD EA for Medical Research for Prevention, Mitigation, and Treatment of Blast Injuries, consistent with Reference (a), to coordinate and manage relevant DoD research efforts and programs, and in that role shall:

5.3.1. Give full consideration to the Research and Engineering (R&E) needs of the DoD Components and the Director, JIEDDO, addressing those needs/requirements by:

5.3.1.1. Maintaining a DoD technology base for medical research related to blast injuries and based on the DDR&E-approved program for the DoD Components.

5.3.1.2. Performing programming and budgeting actions for all blast-injury research to maintain the R&E programs based on DDR&E-approved priorities of the DoD Components.

5.3.1.3. Programming and budgeting for blast-injury research based on analysis and prioritization of needs of the DoD Components, consistent with paragraph 5.1 of this Directive.

5.3.1.4. Executing the approved DoD blast-injury research program consistent with DoD guidance and availability of annual congressional appropriations.

5.3.2. Provide medical recommendations with regard to blast-injury prevention, mitigation, and treatment standards to be approved by the ASD(HA).

5.3.3. Coordinate DoD blast-injury-research issues with the staffs of the DDR&E, the ASD(HA), and the Director, JIEDDO.

5.3.4. Support the development, maintenance, and usage of a joint database for collection, analysis, and sharing of information gathered or developed by the DoD Components related to the efficacy of theater personal protective equipment (including body armor, helmets, and eyewear) and vehicular equipment designed to protect against blast injury.

5.3.5. Appoint a medical general or flag officer representative to the ASBREM Committee.

5.3.6. Ensure that information is shared as broadly as possible except where limited by law, policy, or security classification and that data assets produced as a result of the assigned responsibilities are visible, accessible, and understandable to the rest of the Department as appropriate and in accordance with Reference (e).

5.4. The Secretaries of the Navy and the Air Force shall:

5.4.1. Forward their respective approved blast-injury medical R&E requirements to the DoD EA for consideration and integration.

5.4.2. Appoint medical general or flag officer representatives to the ASBREM Committee and appoint representatives to any other coordination, oversight, or assessment board established by DDR&E or the DoD EA.

5.4.3. Coordinate with other DoD Components on the assignment of Joint Technical Staff Officers to Army medical research entities, research and acquisition organizations, or installations for coordination of research programming and execution needs pertaining to their Component.

5.4.4. Provide an appropriate system for identification, verification, prioritization, and headquarters-level approval of their respective blast-injury R&E requirements before submission to the DoD EA.

5.5. The President of the Uniformed Services University of the Health Sciences (USUHS), under the ASD(HA) and USD(P&R), shall:

5.5.1. Ensure that education relating to blast-injury prevention, mitigation, and treatment is included in the USUHS medical and continuing education curriculum and programs.

5.5.2. Appoint a representative to any coordination, oversight, or assessment board established by DDR&E or the DoD EA.

5.6. The Chairman of the Joint Chiefs of Staff shall:

5.6.1. Coordinate input to the DoD EA and ensure integration of the requirements processes of the Joint Capabilities Integration and Development System [2] with the processes employed under this Directive.

5.6.2. Appoint a relevant senior representative to the ASBREM Committee.

5.6.3. Appoint representatives to organizational entities of the ASBREM Committee and to any other coordination, oversight, or assessment board established by DDR&E or the DoD EA.

5.7. The Commander, US Special Operations Command shall establish procedures and processes for coordination of relevant Defense Major Force Program 11 activities with those planned, programmed, and executed by the DoD EA and shall also:

5.7.1. Forward that command's approved blast-injury R&E requirements for consideration and integration to the DoD EA.

5.7.2. Appoint representatives to organizational entities of the ASBREM Committee, as appropriate, and to any other coordination, oversight, or assessment board established by DDR&E or the DoD EA.

5.7.3. Coordinate with the command on the assignment of Joint Technical Staff Officers to Army medical research entities, research and acquisition organizations, or installations for coordination of research programming and execution needs.

5.7.4. Provide an appropriate system for identification, verification, and headquarters-level approval of that command's blast-injury R&E requirements before submission to the DoD EA.

5.8. The Director, JIEDDO, consistent with Reference (f), shall:

5.8.1. Support development, maintenance, and usage of a joint database for collection, analysis, and sharing of information gathered or developed by DoD Components related to the efficacy of theater personal protective equipment (e.g., body armor, helmets, and eyewear) and vehicular equipment designed to protect against blast-injury.

5.8.2. Appoint representatives to organizational entities of the ASBREM Committee, as appropriate, and to any other coordination, oversight, or assessment board established by DDR&E or the DoD EA.

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2 8CJCSI 3170.01E, "Joint Capabilities Integration and Development System," May 11, 2005, is available at http://.dtic.mil/cjcs_directives/cjcs/instructions.htm.

5.8.3. Assist the DoD EA, the DDR&E, and the ASD(HA) with identification of related operational and research needs, assessment of relevant research efforts, and coordination of planning to resolve capability gaps through focused research efforts.

6. AUTHORITY

The DoD EA identified by this Directive is hereby delegated authority to do the following:

6.1. Obtain reports and information, consistent with the policies and criteria of DoD Directive 8910.1 (Reference (g)), as necessary, to carry out assigned responsibilities and functions.

6.2. Communicate directly with the Heads of the DoD Components, as necessary, to carry out assigned functions, including the transmission of requests for advice and assistance. Communications to the Military Departments shall be transmitted through the Secretaries of the Military Departments, their designees, or as otherwise provided in law or directed by the Secretary of Defense in other DoD issuances. Communications to the Commanders of the Combatant Commands shall normally be transmitted through the Chairman of the Joint Chiefs of Staff.

6.3. Communicate with other Federal Agencies, representatives of the Legislative Branch, members of the public, and representatives of foreign governments, as appropriate, in carrying out assigned responsibilities and functions. Communications with representatives of the Legislative Branch shall be coordinated with the Assistant Secretary of Defense for Legislative Affairs and the Under Secretary of Defense (Comptroller)/Chief Financial Officer, as appropriate, and be consistent with the DoD Legislative Program.

Gordon England

7. EFFECTIVE DATE

This Directive is effective immediately.

E1. ENCLOSURE 1

REFERENCES, continued

(e) DoD Directive 8320.2, "Data Sharing in a Net-Centric Department of Defense," December 2, 2004
(f) DoD Directive 2000.19E, "Joint Improved Explosive Device Defeat Organization (JIEDDO)," February 14, 2006
(g) DoD Directive 8910.1, "Management and Control of Information Requirements," June 11, 1993

E2. ENCLOSURE 2

TAXONOMY OF INJURIES FROM EXPLOSIVE DEVICES

E2.1.1. Primary. Blast overpressure injury resulting in direct tissue damage from the shock wave coupling into the body.

E2.1.2. Secondary. Injury produced by primary fragments originating from the exploding device (preformed and natural (unformed) casing fragments, and other projectiles deliberately introduced into the device to enhance the fragment threat); and secondary fragments, which are projectiles from the environment (debris, vehicular metal, etc.).
E2.1.3. Tertiary. Displacement of the body or part of body by the blast overpressure causing acceleration/deceleration to the body or its parts, which may subsequently strike hard objects causing typical blunt injury (translational injury), avulsion (separation) of limbs, stripping of soft tissues, skin speckling with explosive product residue and building structural collapse with crush and blunt injuries, and crush syndrome development.

E2.1.4. Quaternary. Other "explosive products" effects—heat (radiant and convective), and toxic, toxidromes from fuel, metals, etc.—causing burn and inhalation injury.

E2.1.5. Quinary. Clinical consequences of "post detonation environmental contaminants" including bacteria (deliberate and commensal, with or without sepsis), radiation (dirty bombs), tissue reactions to fuel, metals, etc.

APPENDIX D:

SUPPLEMENTAL TABLES

TABLE D-1: FY18 CDMRP Research Programs with Blast Injury-Related Research Activities

CDMRP Research Program	Program Focus
Defense Medical Research and Development Program (DMRDP)	The **DMRDP** provides execution management support for the six DHP core research program areas. Each of these major research program areas is strategically guided by a committee, called a Joint Program Committee (JPC), which consists of DoD and non-DoD medical and military technical experts. The CDMRP provides program and award management support primarily for basic through translational research (Program Elements 6.1 through 6.3) and also works closely with the JPCs to transition products to advanced development. Example focus areas relevant to blast injury: • Develop and field sensors to characterize the potentially injurious environments Soldiers are exposed to during training • Elucidate the complex relationship between vision and TBI, recovery, and impact quality of life • Development and preclinical testing of novel chemotypes as therapies for wound infection
Epilepsy Research Program (ERP)	The **ERP** funds research to develop an understanding of the magnitude of post traumatic epilepsy (PTE) within the military and to expand research into the basic mechanisms by which TBI produces epilepsy. Example focus areas relevant to blast injury: • Epidemiological characterization and identification of risk factors for developing PTE following TBI • Identification of markers or mechanisms that address PTE • Development of new models or better characterization of existing models for PTE, including repetitive TBI
Joint Warfighter Medical Research Program (JWMRP)	The **JWMRP** funds mature research projects close to yielding tangible benefits to military medicine. The JWMRP focuses on six program areas: Medical Simulation and Information Sciences, Military Infectious Diseases, MOM, CCC, Radiation Health Effects, and CRM. Example focus areas relevant to blast injury: • Simulation technology and medical training • Prophylactics and novel therapeutics to treat multi-drug resistant organisms in combat wound infections, countermeasures that prevent and mitigate Service member injury • Development and validation of effective evidenced-based prevention, screening and assessment strategies, as well as treatment and rehabilitation interventions for concussion/mTBI • Identification and development of medical techniques and materiel (medical devices, drugs, and biologics) for early intervention in life-threatening battle injuries • Neuromusculoskeletal injury (including amputees), sensory systems (including balance, vision, and hearing), acute and chronic pain, and regenerative medicine

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CDMRP Research Program	Program Focus
Military Burn Research Program (MBRP)	The **MBRP** funds projects that support a broad research portfolio in the treatment of burns and the trauma associated with burn injuries sustained during combat or combat-related activities. Example focus areas relevant to blast injury: • Investigation of the impact of various fluid resuscitation techniques on clinically relevant outcomes during acute burn resuscitation • Studies on single or multiple organ failure in the burn/trauma patient • Evaluation of factors involved in burn wound healing and optimization of strategies for treatment • Impact of prolonged field care and delayed evacuation on patient outcomes
Orthotics and Prosthetics Outcomes Research Program (OPORP)	The **OPORP** funds research that evaluates the comparative effectiveness of orthotic and prosthetic clinical interventions and/or their associated rehabilitation interventions, using patient-centric outcomes for Service members and Veterans who have undergone limb impairment or limb amputation. Example focus areas relevant to blast injury: • Determination of optimal timing for prosthetic/orthotic intervention and selection of optimal device • Evaluation of comparative effectiveness of different orthotic devices as well as prevention of secondary adverse consequences from prosthetic/orthotic use • Application of specific rehabilitation interventions to accelerate the time, course, or extent of functional outcomes
Peer Reviewed Medical Research Program (PRMRP)	The **PRMRP** funds research across the entire spectrum of medical research toward improving the health and well-being of Service members, Veterans, and their Families. Example focus areas relevant to blast injury: • Post traumatic headache • DNA vaccine technology for postexposure prophylaxis • Neuroprosthetics • Post traumatic osteoarthritis • Tinnitus
Peer Reviewed Orthopaedic Research Program (PRORP)	The **PRORP** funds research to advance the treatment of and rehabilitation from musculoskeletal injuries sustained in combat. The PRORP seeks to optimize recovery and restoration of function following orthopaedic injuries. Example focus areas relevant to blast injury: • Decreasing secondary health effects of reduced mobility following non-spinal cord traumatic neuromusculoskeletal injury • Comparative evaluation of physical/occupational therapy regimens to achieve optimal rehabilitation • Prevention of surgical site/amputation site neuromas • Development of novel materials and technologies to improve performance of prosthetics and orthotics • Development of osseointegration for upper extremity prostheses • Techniques for healing blast-related segmental bone injuries, in which large pieces of bone are lost

CDMRP Research Program	Program Focus
Psychological Health and TBI Research Program (PH/TBIRP)	The **PH/TBIRP** funds research efforts aimed at improving prevention, detection, and treatment of psychological health disorders and TBIs. Research funded by PH/TBIRP spans the translation research spectrum from basic research to clinical trials. The CDMRP provides program and award management support for PH/TBIRP funds. Example focus areas relevant to blast injury: • Investigations of blast physics for improved understanding of mechanism and for enhanced design of PPE • Comparison of behavioral and neural pathologies in blast-induced and mechanically-induced TBI • Evaluation of rehabilitative therapies for TBI injury, including telerehabilitation and virtual reality • Evaluation of neuroprotective and/or therapeutic compounds to treat TBI • Development of field-ready diagnostic devices for PTSD and TBI
Reconstructive Transplant Research (RTR) Program	The **RTR Program** funds innovative research that will foster new directions for, and address neglected issues in, the field of reconstructive transplantation, specifically for vascularized composite allotransplantation (VCA)-focused research. Example focus areas relevant to blast injury: • Immune system regulation • Improved access to reconstructive transplantation • Reconstructive transplantation rehabilitation • Graft surveillance—clinical monitoring • Psychosocial issues associated with VCA
Spinal Cord Injury Research Program (SCIRP)	The **SCIRP** funds collaborative research to advance the treatment and rehabilitation of SCI. Example focus areas relevant to blast injury: • Management of acute SCI care (pre-hospital, en route care, and early hospital management) • Best practices for rehabilitation and adjustment to SCI • Research towards the development of spinal regeneration • Secondary health effects and complications following SCI • Investigation and improvement of functional deficits
Vision Research Program (VRP)	The **VRP** funds research efforts to improve and transform the care of military personnel affected by diseases and injuries of the eye. The program focuses on funding innovative, military-relevant research that addresses unmet clinical needs. Example focus areas relevant to blast injury: • Mitigation and treatment of traumatic ocular and visual system injuries • Treatment of TBI-induced visual dysfunction, including that caused by direct blast injury • Strategies for the protection, prevention, and rehabilitation of eye injuries • Epidemiological studies of military eye trauma, including TBI-induced visual dysfunction

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